BMI and outcomes of endometrial and ovarian cancer patients

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INTRODUCTION AND OUTLINE OF THE THESIS

Introduction

Gynaecological cancers account for approximately 10% of all cancer diagnosed in women in the United Kingdom. Of these, endometrial cancer and ovarian cancer (including fallopian tubes and primary peritoneal cancer) are the most prevalent with more than 15.500 new cases diagnosed in 2012 (1). While the incidence of other cancers have levelled or declined in the last decades, rates of endometrial cancer and ovarian cancer are increasing (2, 3). One of the main reasons for this is the obesity epidemic, which continues to escalate in developed countries and has resulted in 32% of women in the United Kingdom being overweight and 25% being obese (4, 5).

Endometrial cancer

The majority of endometrial cancer patients are diagnosed with early stage disease (FIGO stage I/II, Table 1) due to early presentation of the disease in the form of postmenopausal bleeding or irregular pre- and peri-menopausal bleeding (6, 7). Two types of endometrial cancer are distinguished based on histopathology and clinical outcomes. Type I tumours comprise 80% of all endometrial cancers and are caused by an unopposed estrogen stimulation leading to endometrioid adenocarcinomas, and are often preceded by glandular hyperplasia of the endometrium. Type II tumours exhibit a non-endometrioid histology, are generally less well differentiated and have a relatively poorer prognosis compared to the endometrioid carcinoma (6).

Table 1 Cancer of corpus uteri FIGO stages (2009)

FIGO stage	
I	Tumour confined to corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumour invades the cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumour
IIIA	Tumour invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal involvement and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Metastases to pelvic nodes
IIIC2	Metastases to para-aortic nodes
IV	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes

Endometrial cancer was the first cancer to be recognised as being related to obesity, with an estimated 34% being attributed to excess weight and obesity (8). The mechanisms through which obesity increases endometrial cancer risk involve both endocrine and metabolic pathways. Obese women have higher estrogen and androgen levels due to the conversion of androstenedione in peripheral adipose tissue. This leads to constant stimulation of the endometrium and the resulting transformation to hyperplasia and cancer. Other mechanisms include insulin resistance and elevated insulin and glucose levels, increased levels of the adipose-derived hormone leptin, and possibly inflammation (9, 10).

The standard treatment of endometrial cancer consists of a primary hysterectomy and bilateral salpingo-oophorectomy, which can be performed through open surgery, minimal invasive approaches (laparoscopic or robotic) or vaginally. Lymphadenectomy is not part of routine practice with low grade tumours, but may be performed in high grade disease or non-endometrioid histology. Adjuvant treatment is tailored according to stage, grade and histology, with adjuvant radiotherapy (brachytherapy and/or external beam) used in patient with intermediate and high risk disease confined to the corpus uteri, or when the disease has extended beyond the corpus uteri (FIGO stage II-IV). Chemotherapy is considered in patients with stage II-IV disease, and may be an option for stage I, grade 3 disease with adverse risk factors (age, lymphovascular space invasion and high tumour volume) (6).

Ovarian cancer

Ovarian cancer usually presents as advanced stage disease (FIGO stage III/IV, Table 2) due to the late onset of symptoms (11, 12). Over 90% of ovarian tumours arise from epithelial cells, while a minority originate from non-epithelial cells and include germ cell tumours or sex-chord stromal tumours (12, 13). The exact cause of ovarian cancer remains unknown, although several risk factors and associated gene mutations have been identified (12).

In ovarian cancer, only 4% of cases have been attributed to overweight and obesity (8). The exact obesity-mediated pathological pathways are less well understood compared to endometrial cancer, but it is believed to be mediated through increased estrogen levels, which stimulate the growth of ovarian cells. Furthermore, hyper-insulinemia and higher levels of insulin-like growth factors, androgens and leptin, which are associated with obesity, have been proposed as additional mechanisms (14).

The standard care for ovarian cancer usually consists of surgery and platinum-based cytotoxic chemotherapy. The aim for surgery in presumed stage I disease is to remove the tumour and perform an appropriate staging procedure. In advanced stage ovarian cancer (II-IV), the aim is to remove all visible disease, as this is an important prognostic factor for survival (12, 15). Chemotherapy is recommended for all patients with stage II-IV disease post-surgery, and may be considered for

Table 2 Ovarian cancer FIGO stages (2013)

FIGO stage	
I	Tumour confined to the ovaries or fallopian tube(s)
IA	Tumour limited to 1 ovary (capsule intact) or fallopian tube, no tumour on ovarian of fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes, no tumour on ovarian of fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC	Tumour limited to 1 or both ovaries or fallopian tubes with any of the following:
IC1	- Surgical spill intraoperatively
IC2	- Capsule rupture before surgery or tumour on ovarian or fallopian tube surface
IC3	- Malignant cells in the ascites or peritoneal washings
II	Tumour invades 1 or both ovarian or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB	Extension to other pelvic intraperitoneal tissues
III	Tumour invades 1 or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA	Positive retroperitoneal lymph nodes only
IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
IV	Distant metastasis excluding peritoneal metastases
IVA	Pleural effusion with positive histology
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

intermediate and high-risk stage I disease. Neoadjuvant chemotherapy with interval surgery has been proposed as an alternative to primary surgery (16-18). Unlike endometrial cancer, radiotherapy does not play a role in the management of primary ovarian cancer (12).

Over the years there have been significant advances in treatment and consequently survival. However ovarian cancer survival remains poor with a 5-year survival of 46%, compared to a 5-year survival of 79% for endometrial cancer (19).

Patient reported outcomes have received increasing interest over the past years, causing current practise to evolve beyond clinical endpoints to include quality of life (QoL) as important outcomes for cancer patients (20). It is well established that cancer diagnosis and treatment have a significant impact on the QoL, and that these effects may persist well into the patients' survivorship years (21).

In the United Kingdom, the majority of endometrial and ovarian cancer patients are overweight (body mass index (BMI) 25-29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) (22, 23). There have been studies suggesting an adverse effect of obesity on cancer treatment and a negative impact on endometrial and ovarian cancer survivorship, but the magnitude of this effect remains unclear (22, 23). In addition, gynaecological oncologists are increasingly treating women within the obese, morbidly obese (BMI ≥ 40 kg/m^2) and even super obese classifications (BMI ≥ 50 kg/m^2), but clear clinical guidance for this group of women remains unavailable.

This thesis will evaluate the effect of body mass index on treatment and quality of life outcomes of endometrial and ovarian cancer patients, and assess the effect of lifestyle interventions as a means to improve quality of life.

Outline of the thesis

Endometrial cancer is the most common gynaecological cancer and surgery is one of the cornerstones of curative treatment. **Chapter 2** discusses the effect of BMI on the surgical outcomes of endometrial cancer patients. Radiotherapy plays an important role in adjuvant treatment of endometrial cancer and in **Chapter 3** we assess the impact of BMI on radiotherapy toxicities and complications.

Quality of life has been recognised as an important outcome of cancer survivors. With the majority of endometrial cancer patients being obese, we assess the influence of BMI on the QoL of survivors in our institution and through a review of the literature in **Chapter 4**.

Chronic inflammation is known to play a role in the process of carcinogenesis and has been linked to obesity. In **Chapter 5** we have evaluated the association between inflammatory markers and obesity, and their prognostic value in endometrial cancer.

Although the relationship between ovarian cancer and obesity is less pronounced compared to endometrial cancer, the reality is that the majority women in the United Kingdom are overweight or obese. For this reason, in **Chapter 6** we describe the impact of BMI on surgical treatment and outcomes of ovarian cancer surgery.

In **Chapter 7 and 8** we have described the effect of excess weight on the QoL outcomes of ovarian cancer survivors at our institution. As physical activity is closely correlated with weight, we have assessed the effect of physical activity in relation to BMI and the QoL of ovarian cancer survivors in a two-centre study (**Chapter 8**).

In **Chapter 9** we review the evidence for the effect of lifestyle interventions to improve the QoL of endometrial and ovarian cancer survivors. As a result, we have suggested guidance for future interventions, which has led us to the development of a feasibility intervention study at our institution, which is outlined in **Chapter 10**.

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Endometrial cancer

2

BMI AND SURGICAL OUTCOMES IN ENDOMETRIAL CANCER PATIENTS – AN INSTITUTIONAL STUDY AND SYSTEMATIC REVIEW

F Bouwman, A Smits, A Lopes, N Das, A Pollard, L Massuger, R Bekkers, K Galaal
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Abstract

Objectives

We aimed to evaluate the association between body mass index (BMI), perioperative complications and outcomes in endometrial cancer (EC) patients at our institution. In addition, we performed a systematic review to compare our results to the literature.

Methods

This was a retrospective study of surgically managed EC patients between January 2006 and January 2015. Patient characteristics, surgical complications and intra- and postoperative outcomes were evaluated across BMI groups; BMI <30 kg/m^2, BMI ≥ 30 kg/m^2 and BMI ≥ 40 kg/m^2. The systematic review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Results

In total, we identified 627 women of which 514 were included; 249 women had a BMI <30 kg/m^2, 195 women had a BMI 30-39.9 kg/m^2, and 70 women were morbidly obese (BMI ≥ 40 kg/m^2). Obese women (BMI ≥ 30 kg/m^2) had significantly more postoperative surgical complications, including wound complications and antibiotics use, which was confirmed by the systematic review. The increase in complications mainly occurred in open surgery and morbidly obese patients were at highest risk. Obesity did not impact other outcomes including 30-day mortality.

Conclusion

Obesity is associated with an increased risk of surgical morbidity in EC patients, and is most profound in open surgery and among the morbidly obese. Laparoscopic surgery may well prevent the majority of postoperative complications in this group of patients, and should therefore be the favoured approach.

Background

Endometrial cancer (EC) is the most common gynaecological malignancy in the UK, with over 8000 women being diagnosed annually (1). The incidence has risen over the recent decades, most likely due to increasing obesity (2, 3), with studies reporting up to 81% of EC patients being obese, and 19% to 36% being morbidly obese (4, 5). Furthermore, the majority of these women are insufficiently active and have several medical obesity-related comorbidities (6, 7). This poses significant challenges for EC management and has been suggested to negatively influence long-term outcomes (8, 9).

Surgery is the cornerstone of EC treatment, and obesity may have an effect on morbidity and outcomes in EC surgery. A recent study identified EC patients with a body mass index (BMI) of ≥40 kg/m^2 being at increased risk of developing surgical complications compared to their non-obese counterparts (10). However, other studies have failed to show any association between BMI and surgical morbidity (11, 12).

As the global obesity epidemic continues to grow, it is important to improve our understanding of the impact of BMI on surgical complications and outcomes in EC (3). This may help identify patients at risk prior to surgery and develop guidelines for clinical care to minimise adverse outcomes. Therefore, we have evaluated the impact of BMI on perioperative complications and outcomes in EC patients at our institution, and performed a systematic review to compare our results to that in the literature.

Methods

Primary study

Design and setting

We performed a retrospective cohort study of surgically managed EC patients at the Royal Cornwall Hospital Trust (RCHT). The study population consisted of women who underwent surgery for EC between January 2006 and January 2015. During this period, surgical management shifted from open approach to laparoscopic approach. We excluded women with insufficient data on their perioperative course, or an unknown preoperative BMI. Ethical approval was obtained through the London – Fulham Ethical committee and the study had full hospital approval.

Data collection

Patients were identified through the cancer registry of the South West Intelligence Service. Patients' medical records were reviewed to collect baseline, clinical and treatment characteristics. BMI was calculated from recorded preoperative height and weight and categorised according to national guidelines (3).

Outcomes

The primary outcome was perioperative morbidity, defined as all complications occurring during surgery and within the first 30 days after surgery. Complications were evaluated individually and subsequently graded according to the Clavien-Dindo classification (13). Wound problems were defined as wound infection, dehiscence, and delayed healing requiring additional care. Antibiotics use entailed the use of an antibiotic for any type of infection, excluding prophylactic treatment. In addition, we assessed secondary outcomes such as hospital stay, estimated blood loss (EBL), transfusion requirements, conversion to laparotomy in laparoscopic cases, and 30-day mortality. Outcomes were compared across the following BMI groups: <30 kg/m^2, 30-39.9 kg/m^2, and ≥ 40 kg/m^2.

Statistical analysis

Data were analysed with IBM SPSS statistical software (14). Means and standard deviations were calculated for continuous variables. Data were compared using the Kruskal-Wallis test or Median test for continuous data, and the Pearson Chi-square test and the Fisher's Exact test for categorical data. Logistic regression models were used while controlling for possible confounders. P-values less than 0.05 were considered significant.

Systematic review

Search strategy and selection criteria

This review was done according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (15), and in accordance with the principles outlined in the Cochrane Handbook (16). Eligible for inclusion were all study designs evaluating the primary association between BMI and surgical complications in EC patients.

Participants; adult women undergoing open or laparoscopic surgery for all stage EC.

Primary outcome; surgical morbidity in terms of complications.

Secondary outcomes: other surgical outcomes including operating time (OR time), EBL, hospital stay, transfusion and conversion to laparotomy.

We performed systematic searches in Medline (1946 until May 2015), Embase (1980 until May 2015), and the Cochrane Trial Register. Search strategies were adapted accordingly (Appendix 1).

Data collection and analysis

Selection of studies

Two reviewers (AS and KG) assessed titles and abstracts of studies independently. Potentially relevant studies were retrieved in full text, and were further reviewed for eligibility by both reviewers. The risk of bias instrument recommended by the Cochrane

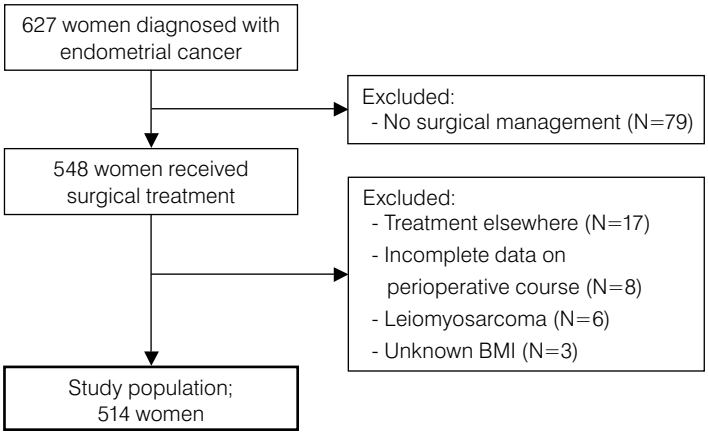
Non-Randomised Studies Methods Group was used for non-randomised comparative studies (17). Additionally, main confounders were identified a priori and included age, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, stage and grade of disease, type and approach of surgery.

Results

Primary study

A total of 627 EC patients were identified, of which 548 patients had undergone surgical management. Excluded were 17 women who received treatment elsewhere, eight women with incomplete data on their perioperative course, six women with leiomyosarcoma, and a further three women with an unknown BMI preoperatively. Consequently, our study population consisted of 514 patients (Figure 1).

Figure 1 Flow chart of recruitment



Characteristics of the study population are summarised in Table 1. The median age was 66 years with a range of 27 – 93 years. Ninety-nine patients (19.3%) had a BMI <25 kg/m^2, 150 patients (29.2%) were overweight, 195 patients (37.9%) had a BMI 30-39.9 kg/m^2, and 70 patients (13.6%) were morbidly obese. Two women were underweight and were included in the BMI <25 kg/m^2 group. Most patients were diagnosed with stage I disease (83.7%). Obese women were more likely to be younger (P=0.005) and the proportion of early stage disease increased with escalating BMI (P=0.004). Furthermore, a higher BMI was associated with a worse ECOG status

Table 1 Baseline and clinical characteristics according to BMI groups

	BMI <30 kg/m² N=249		BMI 30-39.9 kg/m² N=195		BMI ≥40 kg/m² N=70		Analysis P-value
Age							0.005*
Median (range)	67	(31-93)	65	(35-88)	63	(27-83)	
ECOG							<0.001*
0	162	(65.1%)	117	(60.0%)	23	(32.9%)	
1	36	(14.5%)	35	(17.9%)	24	(34.3%)	
2-4	14	(5.6%)	14	(7.2%)	12	(17.1%)	
Unknown	37	(14.9%)	29	(14.9%)	11	(15.7%)	
Smoking status							0.675
Yes	23	(9.2%)	13	(6.7%)	6	(8.6%)	
No	224	(90.0%)	182	(93.3%)	64	(91.4%)	
Unknown	2	(0.8%)	0	(0%)	0	(0%)	
Comorbidities							0.001*
None	67	(26.9%)	38	(19.5%)	7	(10.0%)	
One	66	(26.5%)	37	(19.0%)	12	(17.1%)	
Two or more	115	(46.2%)	119	(61.0%)	51	(72.9%)	
Unknown	1	(0.4%)	1	(0.5%)	0	(0%)	
Stage							0.004*
1	191	(76.7%)	171	(87.7%)	68	(97.1%)	
2	23	(9.2%)	10	(5.1%)	1	(1.4%)	
3	24	(9.6%)	10	(5.1%)	1	(1.4%)	
4	10	(4.0%)	4	(2.1%)	0	(0%)	
Unknown	1	(0.4%)	0	(0%)	0	(0%)	
Grade							0.019*
1	81	(32.5%)	70	(35.9%)	32	(45.7%)	
2	82	(32.9%)	74	(37.9%)	28	(40.0%)	
3	83	(33.3%)	51	(26.2%)	10	(14.3%)	
Unknown	3	(1.2%)	0	(0%)	0	(0%)	
ASA							<0.001*
1 + 2	192	(77.1%)	146	(74.9%)	27	(38.6%)	
3 + 4	39	(15.7%)	42	(21.5%)	38	(54.3%)	
Unknown	18	(7.2%)	7	(3.6%)	5	(7.1%)	
Type of surgery							0.560
Open	129	(51.8%)	110	(56.4%)	36	(51.4%)	
Laparoscopic	118	(47.4%)	81	(41.5%)	33	(47.1%)	
Vaginal	2	(0.8%)	4	(2.1%)	1	(1.4%)	
Time since diagnosis							0.495
Mean (SD)	48	(32.3)	49	(30.7)	43	(27.7)	

*: P<0.05; ASA: American Association of Anesthesiologists; SD: standard deviation

(P<0.001), more comorbidities (P=0.001), and a higher ASA (American Society of Anesthesiologists) score (P<0.001). Other baseline and clinical characteristics did not differ between the BMI groups.

There were no significant differences in surgical approach among BMI groups (P=0.560). In total, 54% of women underwent an open procedure, which is a reflection of the change in standard management.

BMI and surgical complications

Overall, obese and morbidly obese women experienced significantly more complications than non-obese women (P=0.010; Table 2).

Intra-operative complications

In total, eight patients developed an intra-operative complication, but incidence rates showed no significant difference among BMI groups (Table 2).

Postoperative complications

Obese patients and morbidly obese patients developed more complications when compared to non-obese patients (P=0.005) (Table 2). The severity of complications according to the Clavien-Dindo classification varied significantly among BMI groups (P=0.021), with obese and morbidly obese women having more grade 2-4 complications (P=0.004), which persisted after adjustment for confounders (P=0.001).

There was a significant difference in the incidence of wound complications and antibiotics use among the different BMI groups (P<0.001 and P=0.001). The overall rate of wound complications were 8.7% and 15.7%, for BMI of 30-39.9 kg/m^2 and ≥40 kg/m^2, compared to 2.8% in non-obese patients. The majority of wound problems were infections (89%), ten women experienced wound or fascia dehiscence and three women had wound problems requiring additional care. These differences in wound complications and antibiotics use persisted (P=0.025; OR 3.011 CI 1.145-7.920 and P=0.010; OR 2.116 CI: 1.200-3.731) when comparing the obese groups (BMI ≥30 kg/m^2) to the non-obese group while adjusting for age, ECOG status, comorbidities, American Society of Anesthesiologists (ASA) score, stage and grade of disease. Further analyses evaluating open surgery and laparoscopic surgery groups separately, revealed that the significant increase in wound complications and antibiotics use among obese women occurred in open surgery (P<0.001, P=0.002), but not in laparoscopic surgery (P=0.811, P=0.112). Other complications showed no significant differences overall (Table 2), or according to surgical approach (data not shown). In addition, 30-day mortality did not vary significantly among groups (P=0.732), with an average rate of 0.6%.

Table 2 Surgical complications and outcomes according to BMI groups

	BMI <30 kg/m² N=249	BMI 30-39.9 kg/m² N=195	BMI ≥40 kg/m² N=70	Analysis P-value
Overall complications				0.010*
Yes	47 (18.9%)	57 (29.2%)	23 (32.9%)	
No	202 (81.1%)	138 (70.8%)	47 (67.1%)	
Intra-operative complications				0.197
Yes	5 (2.0%)	1 (0.5%)	2 (2.9%)	
No	244 (98.0%)	194 (99.5%)	68 (97.1%)	
Individual complications				
Bowel injury	2 (0.8%)	0 (0%)	0 (0%)	0.632
Bladder injury	0 (0%)	1 (0.5%)	0 (0%)	0.516
Ureter injury	0 (0%)	0 (0%)	1 (1.4%)	0.136
Vascular injury	1 (0.4%)	0 (0%)	0 (0%)	1.000
Other	2 (0.8%)	0 (0%)	1 (1.4%)	0.259
Postoperative complications				0.005*
Yes	44 (17.7%)	57 (29.2%)	22 (31.4%)	
No	205 (82.3%	138 (70.3%)	48 (68.6%)	
Clavien-Dindo grade				0.021*
1	13 (30.2%)	4 (7.3%)	1 (4.5%)	
2	26 (60.5%)	43 (78.2%)	16 (72.7%)	
3	2 (4.7%)	4 (7.3%)	4 (18.2%)	
4	2 (4.7%)	4 (7.3%)	1 (4.5%)	
Individual complications				
Wound complication	7 (2.8%)	17 (8.7%)	11 (15.7%)	<0.001*
Laparoscopic	1 (0.4%)	1 (0.5%)	0 (0%)	0.811
Open	6 (2.4%)	16 (8.2%)	11 (15.7%)	<0.001*

Ileus	6	(2.4%)	1	(0.5%)	0	(0.0%)	0.176
Antibiotics use	26	(10.4%)	43	(22.1%)	17	(24.3%)	0.001*
Laparoscopic	7	(2.8%)	12	(6.2%)	3	(4.3%)	0.112
Open	17	(6.8%)	31	(15.9%)	13	(18.6%)	0.002*
Urinary tract infection	5	(2.0%)	5	(2.6%)	3	(4.3%)	0.499
Pneumonia	5	(2.0%)	7	(3.6%)	1	(1.4%)	0.623
Pelvic abscess	1	(0.4%)	1	(0.5%)	0	(0%)	1.000
Secondary haematoma	5	(2.0%)	4	(2.1%)	0	(0%)	0.728
Venous thrombo-embolism	3	(1.2%)	0	(0%)	0	(0%)	0.372
Sepsis	1	(0.4%)	1	(0.5%)	0	(0%)	1.000
Renal complication	1	(0.4%)	1	(0.5%)	1	(1.4%)	0.523
Cardiac complication	3	(1.2%)	5	(2.6%)	1	(1.4%)	0.594
Organ failure	2	(0.8%)	4	(2.1%)	0	(0%)	0.430
Relaparotomy	3	(1.2%)	5	(2.6%)	2	(2.9%)	0.413
Other	17	(6.8%)	15	(7.7%)	5	(7.1%)	0.971
30-day mortality	1	(0.4%)	2	(1.0%)	0	(0%)	0.732
90-day mortality	3	(1.2%)	3	(1.5%)	0	(0%)	0.865
Other operative outcomes							
Conversion to laparotomy	7	(5.6%)	16	(16.5%)	9	(21.4%)	0.006*
EBL, mean (SD)							
Laparoscopic	72	(75.7)	116	(110.6)	125	(92.6)	<0.001*
Open	267	(201.8)	290	(272.7)	258	(200.8)	0.901
Transfusion (intra- & post-op)							0.768
Yes	6	(2.4%)	7	(3.6%)	2	(2.9%)	
No	243	(97.6%)	188	(96.4%)	68	(97.1%)	
Hospital stay Mean (SD)	5.1	(3.8)	4.7	(2.5)	4.7	(3.3)	0.722

*: P<0.05; SD: standard deviation

Table 3 Characteristics of included studies in the systematic review

Study	Study design	No	Patients	BMI groups
Akbayir et al. (20)	Retrospective study Open surgery	346	EC (I-IV)	< 25 kg/m² 25-29.9 kg/m² ≥ 30 kg/m²
Erkanli et al. (21)	Retrospective study Open surgery	42	EC (I-IV)	< 30 kg/m² 30-39.9 kg/m² ≥ 40 kg/m²
Everett et al. (22)	Retrospective study Open surgery	396	EC (I-IV)	< 30 kg/m² 30-39.9 kg/m² ≥ 40 kg/m²
Ghezzi et al. (26)	Prospective cohort study Laparoscopic surgery	101	EC (I-IV)	< 30 kg/m² ≥ 30 kg/m²
Gunderson et al. (10)	Ancillary data analysis of RCT Open and laparoscopic surgery	2510	EC (I-IV)	< 25 kg/m² 25-29.9 kg/m² 30-34.9 kg/m² 35-39.9 kg/m² ≥ 40 kg/m²
Kerimoglu et al. (25)	Prospective study Open surgery	94	EC (I-IV)	< 30 kg/m² ≥ 30 kg/m²
Litta et al. (18)	Unknown design Laparoscopic surgery	75	EC (I-IV)	< 30 kg/m² ≥ 30 kg/m²
Mahdi et al. (7)	Retrospective study Open and laparoscopic surgery	3947	EC Stage unknown	18-29.9 kg/m² 30-39.9 kg/m² ≥ 40 kg/m²
O'Hanlan et al. (19)	Retrospective study Laparoscopic surgery	88	EC (I-IV) and hyperplasia	< 18.5 kg/m² 18.5-25 kg/m² 25-29.9 kg/m² 30-39.9 kg/m² ≥ 40 kg/m²

Outcomes measures	Conclusion
1. GIS, vascular and nerve injury 2. Wound infection, hernia, lymphatic complications 3. OR time, EBL, hospital stay	1. NS 2. NS 3. BMI ≥ 30 ↑ OR time
1. Overall rate, ureteral, bowel, bladder and vessel injury 2. Overall rate, wound dehiscence, wound infection, UTI, ileus, DVT, sepsis, pneumonia, cardiac or lymphatic complication, death 3. OR time, EBL, hospital stay, ABT	1. NS 2. BMI ≥ 40 ↑ wound dehiscence 3. BMI ≥ 40 ↑ OR time
1. Overall rate, haemorrhage, ureteral, vessel, bowel and bladder injury, arrhythmia 2. Overall, wound separation, wound infection, UTI, sepsis, pneumonia, ileus, small bowel obstruction, DVT, failed voiding trial, cardiac complication, DVT, mortality 3. OR time, EBL, hospital stay, ICU stay, ABT	1. NS 2. BMI ≥ 40 ↑ wound separation 3. BMI ≥ 40 ↑ OR time and ↑ EBL
1. Overall rate 2. Overall rate 3. OR time, EBL, hospital stay, conversion to laparotomy	1. NS 2. NS 3. NS
1. Overall rate, bowel, vessel, bowel, bladder and ureter injury, others 2. Overall rate, UTI ,fever, pelvic cellulitis, abscess, VTP, PE, bowel obstruction, ileus, pneumonia, wound infection, antibiotics use, urinary fistula, bowel fistula, congestive heart failure, arrhythmia, re-operation, death 3. ABT, hospital stay, readmission	1. NS 2. ↑ BMI ↑ total complications, VTP, wound infection and antibiotics use 3. BMI ≥ 40 ↑ hospital stay
1. Bladder, urethral, vascular or bowel injury 2. Wound infection, ileus, atelectasis, haemorrhage 3. OR time, hospital stay, ABT	1. NS 2. NS 3. NS
1. Overall rate 2. Vaginal cuff dehiscence, DVT, lymphatic complication 3. OR time, EBL, hospital stay	1. NS 2. NS 3. NS
1. Not in article 2. Overall rate, number, surgical complication, non-surgical complication, infection, SSI, wound disruption, peripheral nerve injury, pneumonia, sepsis, septic shock, renal, pulmonary or cardiac complication, re-operation, 30-day mortality 3. OR time, hospital stay, ABT	1. NIA 2. BMI ≥ 40 ↑ total complications, infection, SSI and wound disruption, BMI 30-39.9 ↓ sepsis 3. BMI ≥ 30 ↑ OR time, and ↓ ABT
1&2. Overall rate combined 3. OR time, EBL, hospital stay, ABT	1&2. NS 3. NS

Table 3 Continued

Study	Study design	No	Patients	BMI groups
Pavelka et al. (23)	Retrospective study Open surgery	339	EC (I-IV)	< 30 kg/m^2 30-39.9 kg/m^2 ≥ 40 kg/m^2
Pellegrino et al. (24)	Retrospective study Laparoscopic surgery	75	EC (I-IV)	< 30 kg/m^2 ≥ 30 kg/m^2
Rabischong et al. (11)	Retrospective study Laparoscopic surgery	207	EC (I-IV)	< 30 kg/m^2 ≥ 30 kg/m^2
Santoso et al. (12)	Prospective study Open surgery	233	EC (I-IV)	< 25 kg/m^2 25-29.9 kg/m^2 30-34.9 kg/m^2 ≥ 35 kg/m^2

EC: endometrial cancer; DVT: deep venous thrombosis; GIS: gastrointestinal system; ICU: intensive care unit; NS: not significant; PE: pulmonary embolism; SSI: surgical site infection; UTI: urinary tract infection; VTE; venous thrombo-embolism; VTP: venous thrombo-phlebitis;

Other operative outcomes

In 32 patients, laparoscopic surgery was converted to a laparotomy, and rates were significantly higher among obese and morbidly obese patients (P=0.006). Conversion rate remained significantly higher in patients with BMI ≥30 kg/m^2 after adjustment for other factors including age, ECOG status, comorbidities, ASA score, stage and grade (P=0.004). Furthermore, EBL was significantly higher in both obese and morbidly obese patients undergoing laparoscopic surgery when compared to non-obese patients (P<0.001), which persisted after correction for the above mentioned factors (P=0.002). Other operative outcomes including transfusion requirements and hospital stay did not show significant differences.

Systematic review

The search strategy identified 915 references, and after screening titles and abstracts 46 articles were retrieved in full text and were further assessed for eligibility. Subsequently, 11 studies were considered eligible for this review, and a search of the grey literature identified a further two eligible studies.

Outcome measures	Conclusion
1. Vascular, bladder, bowel or ureteral injury 2. Ileus, wound infection, wound break-down, unspecified febrile morbidity, nerve injury, lymphatic complication, VTE, pneumonia, 30-day mortality 3. OR time, EBL, hospital stay, ABT	1. NS 2. BMI ≥ 40 ↑ wound infection and wound breakdown 3. BMI ≥ 40 ↑ OR time, BMI ≥ 30 ↑ EBL
1. Overall rate 2. Fever, VTE, paraesthesia, cardiac, lymphatic, and renal complications, re-operation, 3. OR time, EBL, hospital stay, ABT, conversion rate	1. NS 2. NIA 3. BMI ≥ 30 ↑ EBL
1. Overall rate, haemorrhage, bladder injury, emphysema, gas embolism 2. Overall rate, hemoperitoneum, phlebitis, PE, intestinal obstruction, vesico-vaginal fistula, lymphatic complication, port-site hernia, obturator neuropathy, vaginal cuff dehiscence, abdominal wall hematoma 3. OR time, hospital stay, ABT, conversion	1. NS 2. NS 3. NS
1. Bowel or bladder injury, obturator vein bleed 2. Fever requiring antibiotics, fascial dehiscence, DVT, UTI, kidney stone, acute renal insufficiency, neurogenic bladder or cardiac complication 3. OR time, EBL, hospital stay, ABT	1. NS 2. NS 3. ↑ BMI ↑ OR time and ↑ EBL

Included studies

The characteristics of the 13 studies included in the review are illustrated in Table 3. Eight studies were retrospective studies and four used prospectively collected data. One study used data from a randomised controlled trial (RCT), in which patients were randomised according surgical approach (10). One study did not define its study design (18). All studies combined resulted in a total of 8453 EC patients. Most studies included all stage EC patients, although one also included women with hyperplasia (N=19) (19), and another did not define which stages of disease were included (7). Six studies evaluated open surgery, five evaluated laparoscopic surgery and two included both open and laparoscopic management.

BMI and intra-operative complications

Almost all articles reviewed the incidence of intra-operative complications except for Mahdi et al. (7). None of the articles found a significant association between BMI and the incidence of overall or individual intra-operative complications.

BMI and postoperative complications

All included studies assessed postoperative complications, with most studies evaluating individual complications (7, 10-12, 18, 20-25). The significant increase in postoperative complications in our study was confirmed by findings of the randomised controlled trial of Gunderson et al., showing a significant increase in the total number of postoperative complications with increasing BMI (10). In addition, the largest retrospective study comprising 3947 patients identified morbidly obese women at increased risk (7).

A significant increase of non-infectious wound complications in morbidly obese women was reported in all retrospective studies including both open and laparoscopic surgery (7, 21-23). However, the association between obesity and wound infection was not uniformly reported. The RCT stated that increasing BMI was associated with a rise in incidence of wound infections, and two retrospective studies combining a total of 4286 women specifically identified morbidly obese women being at increased risk after open surgery (7, 10, 23). In addition, Gunderson et al. reported a significant increase in infection complications after open surgery, a higher incidence of venous thrombo-phlebitis in women with BMI ≥25 kg/m^2, and increased use of antibiotics in the morbidly obese group, concurring with our findings (10). In several studies the association between infectious wound complications and BMI was not apparent. However, they did not include morbid obesity as a separate group, which may explain the lack of uniformity in reporting postoperative wound infections (20, 25).

Other individual complications did not show a significant association with BMI, and no differences were found in postoperative mortality rates, similar to the results of our institutional study (7, 10, 22, 23).

BMI and other operative outcomes

The association between BMI and OR time was assessed by twelve studies. The majority of studies assessing open surgery were of retrospective design. They found that obese women and especially morbidly obese women required significantly longer operating times (7, 20-23), which was also confirmed by the prospective study of Santoso et al. (12). Studies assessing laparoscopic surgery did not report a significant association between operating time and BMI (11, 18, 19, 24, 26).

We found a significant increase in EBL among the obese and morbidly obese in laparoscopic surgery, mirroring the results of Pellegrino et al. (24). Two retrospective studies and one prospective study evaluating open surgery, found a higher EBL with increasing BMI (12, 22, 23). However, four retrospective and one prospective study including both open and laparoscopic surgery failed to show an association (18-21, 26). The increased conversion rates among obese and morbidly obese patients in our study was not found in other studies including a total of 383 patients, but was not evaluated by the RCT (11, 24, 26).

BMI did not affect hospital stay in any study except for the RCT, where a significantly longer stay was reported in the morbidly obese group compared to women with BMI <25 kg/m^2 (10). However, they did not correct for possible confounders such as surgical approach, and its distribution among the BMI groups was not specified (10). Transfusion rates were not associated with BMI in any of the studies (7, 10-12, 19, 21-25).

Risk of bias and confounding

The majority of studies were non-randomised with a retrospective design, leading to a high risk of bias associated with non-randomisation, selective reporting and patient attrition. Only two studies reported on possible confounders and adjusted for this in their analysis. None of the studies reported their complications according to international scoring systems such as the Clavien-Dindo classification. In addition, the majority of studies did not define a timeframe within which the postoperative complications would occur, and several studies did not specify the numbers of complications for each BMI group.

Discussion

Endometrial cancer is strongly associated with obesity, resulting in the majority of patients being obese (27). The aim of this study was to give a comprehensive overview of the current literature on the impact of BMI on the surgical complications and outcomes of EC patients, and to provide guidance for clinical care and future studies.

The institutional study showed that obesity is a risk factor for overall and postoperative surgical complications, including wound complications and increased use of antibiotic treatment specifically after open surgery. The review confirmed our findings of a higher incidence of wound and infectious complications among obese women with EC. In addition, the review showed that the total number of complications increased with BMI, identifying morbidly obese at a particularly high risk. BMI was not associated with other perioperative complications or postoperative mortality, and our rates were consistent with other reported rates (7, 23).

Increasing BMI was significantly associated with longer operating times in open surgery in the review. The increased conversion rates in women with BMI ≥30 kg/m^2 in the institutional study was not confirmed by studies in the review. However, considering the size of our study population and the number of conversions, we believe this requires further assessment by future studies.

We therefore confirm the association between obesity and surgical morbidity in EC, showing that morbidly obese women are especially at significant risk. This

association is more pronounced in the open surgical approach with increased postoperative complications in obese women in both the institutional study and the review. Obese women will therefore benefit most from laparoscopic surgery in terms of postoperative outcomes, and this should be the favoured approach. A recent Cochrane review showed that laparoscopy has similar survival outcomes and reduced operative morbidity compared to laparotomy in EC (28). Furthermore, obese women are not at increased risk of intra-operative morbidity or mortality, contrary to common clinical perception. Still, efforts should be made to minimise adverse outcomes with special attention to this group of patients. Peri-operative complications adversely affect recovery and may delay adjuvant treatment, and should therefore receive due attention. Enhanced recovery programmes have already been proposed but not routinely evaluated in standard practise to improve operative outcomes, and therefore require further assessment (29).

Risk factors for postoperative wound complications are well recognised and extensive precautions are already being undertaken by surgical and anaesthetic teams in terms of skin preparation, suturing techniques, prophylactic antibiotics, tissue perfusion, fluid management and cardiopulmonary support. However, patient-related risk factors including age, smoking, physical and nutritional condition, obesity and comorbidities such as diabetes and cardiovascular disease, still pose significant threats to postoperative wound healing and recovery (30). We therefore recommend the assessment of prehabilitation programmes, comprising the optimisation of patients prior to surgical treatment, to improve modifiable risk factors. Although implementation remains a challenge because of a restricted time period between diagnosis and treatment, previous studies have shown promising results (31-35).

Strengths and limitations

Strengths of the institutional study include the study size, and the inclusion of all histological subtypes and stages, increasing its applicability. Additionally, the internationally validated Clavien-Dindo classification was used for systematic grading of postoperative complications and we corrected for possible confounders. However, our study still has limitations inherent to its retrospective design, including non-randomization, possible selection bias and completeness of previously recorded data.

Completeness and applicability of evidence of the systematic review

The majority of women were diagnosed with stage I disease, consistent with reported incidence rates (36). The studies evaluated a variety of surgical complications of which the majority could be compared.

Quality of evidence

The majority of studies were susceptible to a high risk of bias, mainly because of their retrospective design. Only one study used data collected from a RCT and a further three used prospectively collected data. Most studies did not adjust for possible confounders. In addition, there was a lack of uniformity in reporting surgical morbidity and in categorisation of BMI groups, with several studies not describing BMI ≥40 kg/m^2 as a separate group.

Potential biases in review process

A comprehensive literature search was performed by the reviewers (AS and KG), including a search of the grey literature. Reviewers assessed potentially eligible articles independently, and differences were resolved by appeal to a third reviewer (AL).

Future research

Ideally, prospective designs and large study populations are preferred to further clarify to what extent obesity impacts surgical morbidity and outcomes. Particular attention needs to be paid to the morbidly obese, as they can comprise up to 36% of the EC population and are at highest risk of postoperative complications impairing recovery and possibly long-term outcomes (5). Classification of complications according to internationally validated systems, such as the Clavien-Dindo system, should be highly recommended to improve comparability across studies. Moreover, future studies should focus on minimising adverse outcomes, possibly through prehabilitation programmes and improving postoperative care pathways.

Conclusion

The results of our institutional study and systematic review confirm that obesity is associated with an increased risk of surgical morbidity in EC patients. This association is most profound in open surgery and among the morbidly obese. Laparoscopic surgery may prevent the majority of postoperative complications in this group of patients, and should therefore be advocated for obese women. In addition, we propose the evaluation of prehabilitation programmes as a means to minimise surgical morbidity and improve outcomes of EC patients.

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Appendix 1 – Search Strategy

1. endometrium AND cancer
2. ENDOMETRIUM CANCER
3. endometr* cancer
4. uter* cancer
5. endometr* neoplasm
6. uter* neoplasm
7. endometr* carcinoma
8. uter* carcinoma
9. BODY MASS INDEX
10. OBESITY/ OR MORBID OBESITY
11. BMI
12. body mass index
13. weight
14. obes*
15. quetelet* index
16. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
17. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
18. GYNECOLOGICAL OPERATION/ OR GYNECOLOGY SURGERY
19. surger*
20. operati*
21. 18 OR 19 OR 20
22. POSTOPERATIVE COMPLICATIONS/ OR COMPLICATION
23. PEROPERATIVE COMPLICATION
24. operative complication*
25. surg* complication*
26. complication*
27. postoperative complication*
28. operative morbid*
29. surg* morbid*
30. DEATH
31. death.
32. mortality
33. morbidity
34. SURVIVAL
35. survival
36. operative outcom*
37. surg* outcom*
38. 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37
39. 16 AND 17 AND 21 AND 38


2

3

BMI AND RADIOTHERAPY TOXICITIES IN ENDOMETRIAL CANCER: ARE OBESE WOMEN AT A DISADVANTAGE?

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Submitted

Abstract

Objective

To assess the impact of body mass index (BMI) on radiotherapy toxicities in endometrial cancer patients.

Methods

This was a retrospective cohort study of women diagnosed with endometrial cancer between January 2006 and December 2014 at the Royal Cornwall Hospital Trust. Women who received radiotherapy as part of treatment, including external beam radiotherapy (EBRT) and/or vaginal brachytherapy were included. Radiation-related toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) guidelines. Toxicity outcomes were compared across BMI groups; non-obese (BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2), according to radiotherapy treatment received (EBRT, brachytherapy or a combination).

Results

A total of 159 women received radiotherapy of which 110 could be included. Sixty-three women had a BMI < 30 kg/m^2 and 47 women were obese. Obese women had poorer ECOG performance status ($P=0.021$) and more comorbidities ($P<0.001$) compared to the non-obese group. Overall toxicity rates were 60.3%, 72.7% and 52.0% for EBRT and brachytherapy ($N=63$), single mode EBRT ($N=22$) and brachytherapy ($N=25$) respectively. BMI was not associated with the incidence of acute and late radiation toxicities in the different radiotherapy groups. There were no differences in individual complications between the BMI groups.

Conclusion

Obesity does not negatively impact the incidence of radiation toxicities in endometrial cancer. However, toxicities remain an important challenge as they are common and negatively influence the quality of life (QoL) of survivors. Future studies need to further explore the role of possible interventions to improve toxicities and QoL.

Background

Endometrial cancer (EC) is the most common gynaecological cancer, affecting more than 8000 women annually in the United Kingdom (1). Radiotherapy plays an important role in the management of EC, with vaginal brachytherapy and/or pelvic external beam radiotherapy (EBRT) being part of treatment of all stages of the disease (2). Evidence supports the use of radiotherapy to significantly reduce tumour relapse rates, although this may not result in an overall survival benefit in early stage disease (3-6). Treatment-related toxicities occur frequently, with reported rates up to 75%, and therefore remain of particular concern as they may severely impact the quality of life (QoL) of survivors (7).

It is important to acknowledge the potential toxicity burden of radiotherapy and to identify possible contributing factors. Toxicity rates have been known to vary among the different radiotherapy modalities, with higher reported rates in EBRT compared to brachytherapy alone (8, 9).

Obesity is an important risk factor for EC, and a significant health issue in the majority of women diagnosed (10, 11). Obesity negatively affects the treatment of EC, with obese women (BMI ≥ 30 kg/m^2) posing significant surgical challenges and having a higher risk of surgical complications (12, 13). However, there is a lack of evidence regarding the effect of obesity on radiotherapy complications, despite radiotherapy being one of the cornerstones of the current adjuvant treatment in EC.

It is important to understand the influence of obesity on radiotherapy management to provide specific clinical guidance for this growing patient group. In this study, we assessed the impact of body mass index (BMI) on radiotherapy toxicities in endometrial cancer patients.

Methods

Study population

This was a retrospective cohort study of women diagnosed with EC between January 2006 and December 2014 at the Royal Cornwall Hospital Trust. We included women with a histological EC diagnosis, who received radiotherapy treatment including pelvic external beam radiotherapy (EBRT), vaginal brachytherapy, or a combination of the modalities. Exclusion criteria were an unknown BMI at time of diagnosis, age ≤ 18 at time of diagnosis, treatment in the palliative setting, and incomplete data on radiotherapy treatment and outcomes. The study had full Trust approval and Ethical approval was obtained through the London – Fulham Ethical committee.

Data collection

Women were identified through the South West Intelligence Service cancer registry. Patients' demographic and clinical characteristics were collected from medical files and included age at diagnosis, marital and smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, FIGO (International Federation of Gynecology and Obstetrics) stage and grade of disease, and treatment. Details of radiotherapy treatment plans included modality (EBRT and brachytherapy), total dose, technique, and EBRT mean dose (Gy) and volume (cm^3) of organs at risk (OAR) including; bladder, bowel, rectum and femurs. BMI at time of diagnosis (weight (kg) / [height (m)]^2) was collected as part of standard practice and categorised into 'non-obese' (BMI $<$ 30 kg/m^2) and 'obese' (BMI $\geq$ 30 kg/m^2).

Technique

Prior to November 2013 patients received EBRT using 3D conformal radiotherapy (3D-CRT), which covered the planned target volume using a 4-field box technique with 10 MV (Mega Voltage) x-rays, with marked coverage of adjacent bladder and bowel. The box technique was based on bony landmarks or planned target volume including lymph node basins and parametrium depending on practise at that time. Bowel was contoured using the bowel bag technique. From November 2013 onwards, EBRT was delivered using Intensity Modulated Radiotherapy (IMRT) using volumetric modulated arc therapy (VMAT) with 6 MV x-rays and on-set Image Guidance Radiotherapy (IGRT). Standard doses varied from 45 to 50.4 Gy in 25-28 fractions over a period of five to 5.5 weeks. Deviations from standard practice included doses of 54 Gy in 30 fractions for pelvic recurrent disease. Vaginal vault brachytherapy was administrated through Low Dose Rate (LDR) brachytherapy or High Dose Rate (HDR) brachytherapy under image guidance. LDR brachytherapy was delivered as 15 Gy in one fraction in conjunction with EBRT, or as a single insertion of 27 to 30 Gy when given as a single mode therapy. HDR brachytherapy was given as single mode treatment consisting of 22 Gy given in four fractions, or in conjunction with doses varying from 5.5 to 8 Gy in 1-2 insertions. From 2014 onwards, all patients received brachytherapy using HDR administration.

Outcomes

Radiation-related toxicities and other reported adverse events were collected from patients' medical records. Toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) guidelines by two clinicians (14). Acute toxicities were defined as toxicities occurring from the start of radiation treatment and within 90 days post-treatment. Late toxicities comprised of toxicities occurring later than three months post-treatment. Toxicities were graded on a scale varying from 0-5, with 0 being no symptoms and 5 being death directly related to radiation effects.

Lymphoedema was not included in the RTOG guidelines, but was considered an important adverse event. Toxicity outcomes were compared across BMI groups; non-obese and obese, according radiotherapy treatment received (EBRT, brachytherapy or a combination). Overall survival (OS) and disease-free survival (DFS) were used for survival comparison. OS was defined as the time from diagnosis to death from all causes. DFS was defined as the time between diagnosis and the first clinical, pathologic or radiographic evidence of loco-regional or distant recurrent disease.

Statistical analysis

Continuous data were presented as means and standard deviations (SD) and were compared using the Mann-Whitney U test. Categorical variables were presented as frequencies and proportions, and compared using the Pearson's Chi-Square and Fisher's exact test. Unknown data were excluded from analysis. Lymphoedema was not included in the RTOG guidelines, but was analysed as a grade ≥ 2 late complication. Survival analyses were performed using the Kaplan-Meier method using the log-rank test. P-values were regarded significant if $P<0.05$ and tests were two-sided. Data analysis was performed using IBM SPSS statistics software (15).

Results

In total, 626 women were diagnosed with EC in the period January 2006 – December 2014. We identified 159 patients who received radiotherapy as part of management. We excluded twenty-four women who received palliative radiotherapy, sixteen women with an unknown BMI, eight women with insufficient follow-up data, and one woman who received her radiotherapy treatment elsewhere. This resulted in a study population of 110 women (Figure 1).

The median age of the study population was 67 years (range 27-84). The majority of women (80%) were diagnosed with early stage disease (I/II). Twenty-eight women had a BMI of < 25 kg/m^2, 35 women were overweight (BMI 25-29.9 kg/m^2) and 47 women were obese (BMI ≥ 30 kg/m^2) at time of diagnosis. Ten women were morbidly obese (BMI ≥ 40 kg/m^2), with five women having a BMI ≥ 45 kg/m^2.

Obese and non-obese women were similar in terms of age, ethnicity, marital and smoking status, and clinical characteristics including stage, grade, treatment and recurrent disease (Table 1). However, obese women had significantly more comorbidities ($P<0.001$) and a poorer ECOG performance score ($P=0.021$) compared to non-obese women.

Figure 1 Flow chart of recruitment

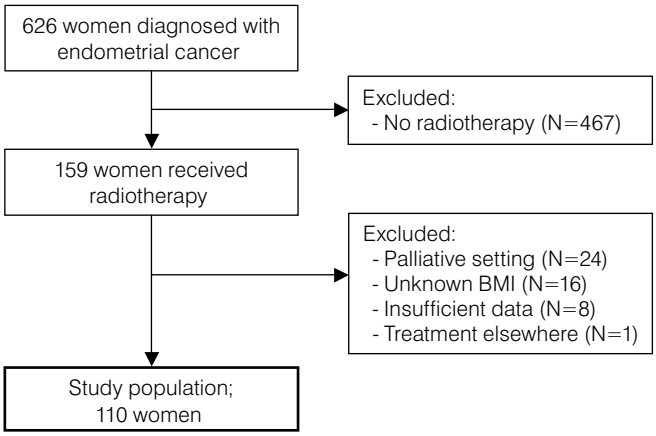

Table 1 Demographic and clinical characteristics according to BMI groups

	BMI < 30 kg/m² N=63		BMI ≥ 30 kg/m² N=47		Analysis P-value
Age					0.721
< 70 years	37	(58.7%)	26	(55.3%)	
≥ 70 years	26	(41.3%)	21	(44.7%)	
Ethnicity					0.506
White	61	(96.8%)	47	(100%)	
Other	2	(3.2%)	0	(0%)	
Marital status					0.860
Married	44	(69.8%)	34	(72.3%)	
Not married	9	(14.3%)	5	(10.6%)	
Widowed	8	(12.7%)	6	(12.8%)	
Unknown	2	(3.2%)	2	(4.3%)	
Comorbidities					<0.001*
None	23	(36.5%)	2	(4.3%)	
One	17	(27.0%)	14	(29.8%)	
Two or more	23	(36.5%)	31	(66.0%)	
ECOG status					0.021*
0	51	(81.0%)	28	(59.6%)	
1	4	(6.3%)	7	(14.9%)	
2-4	1	(1.6%)	5	(10.6%)	
Unknown	7	(11.1%)	7	(14.9%)	

Table 1 Continued

	BMI < 30 kg/m² N=63		BMI ≥ 30 kg/m² N=47		Analysis P-value
Smoking status					0.135
Yes	7	(11.1%)	1	(2.1%)	
No	56	(88.9%)	45	(95.8%)	
Unknown	0	(0%)	1	(2.1%)	
FIGO Stage					0.631
I/II	49	(77.8%)	39	(83.0%)	
III/IV	14	(22.2%)	8	(17.0%)	
Grade					0.232
1	7	(11.1%)	4	(8.5%)	
2	17	(27.0%)	20	(42.6%)	
3	39	(61.9%)	23	(48.9%)	
Surgical treatment					0.575
Yes	62	(98.4%)	45	(95.7%)	
TLH + BSO	25	(39.7%)	12	(25.5%)	
TAH + BSO	37	(58.7%)	33	(70.2%)	
No	1	(1.6%)	2	(4.3%)	
Chemotherapy					0.491
Yes	17	(27.0%)	10	(21.3%)	
No	46	(73.0%)	37	(78.7%)	
Recurrence					0.652
Yes	11	(17.5%)	7	(14.9%)	
Local	4	(6.4%)	4	(8.5%)	
Distant	7	(11.1%)	3	(6.4%)	
No	52	(82.5%)	40	(85.1%)	
Time since diagnosis					0.646
Mean (SD)	59.3 (33.3)		57.0 (33.8)		

SD: standard deviation; *: P<0.05

The majority of women (N=63) received a combination of pelvic EBRT and brachytherapy, 22 women received EBRT and 25 women received brachytherapy. Most women were treated using 3D-CRT (89%). EBRT total doses varied from 45 to 54.0 Gy (median 45.0 Gy). Brachytherapy varied from 8 to 30 Gy, with the exception of one woman who received a single fraction of 5.5 Gy. There was no significant difference in radiotherapy treatment (P=0.170), EBRT and brachytherapy dose (P=0.169, P=0.590), nor the technique used (P=1.000) (Table 2). The mean volume of bowel at risk was significantly higher in the obese group (P=0.014), which is reflected in a significantly lower mean dose received by the bowel in obese women (P=0.002). Other OAR volumes and doses did not significantly differ (Table 2).

Table 2 Radiotherapy details according to BMI groups

	BMI < 30 kg/m² N=63		BMI ≥ 30 kg/m² N=47		Analysis P-value
Radiotherapy treatment					0.170
EBRT	10	(15.9%)	12	(25.5%)	
EBRT + brachytherapy	35	(55.6%)	28	(59.6%)	
Brachytherapy	18	(28.6%)	7	(14.9%)	
EBRT Technique					1.000
3D-Conformal	40	(88.9%)	37	(90.0%)	
IMRT	5	(11.1%)	4	(10.0%)	
EBRT OAR mean volume (cm^3)					
Bladder	145.35	(90.83)	115.81	(64.95)	0.171
Bowel	1597.97	(552.82)	2100.50	(1060.84)	0.014*
Rectum	73.58	(40.69)	76.09	(49.45)	0.702
Femurs	86.61	(16.55)	80.27	(20.43)	0.220
EBRT OAR mean dose (Gy)					
Bladder	42.42	(8.25)	43.77	(9.47)	0.244
Bowel	28.87	(5.73)	25.34	(6.45)	0.002*
Rectum	39.96	(7.69)	39.63	(9.78)	0.835
Femurs	33.36	(7.89)	34.57	(8.55)	0.469

EBRT: external beam radiotherapy; Gy: Gray; OAR: organs at risk; *: P<0.05

The overall toxicity rate in the study population was 60.9%, with an overall rate of 60.3%, 72.7% and 52.0% for EBRT and brachytherapy, single mode EBRT, and brachytherapy respectively. Forty-six women (41.8%) experienced an acute toxicity, of which the 21 women (45.7%) reported a grade 2 toxicity or higher. Data on late toxicities was available for 106 women, as four women were excluded because they died within 90 days after the end of radiotherapy treatment or because of insufficient long-term follow-up data. Thirty-six women (34.0%) experienced a late toxicity, of which the majority (55.6%) were grade ≥ 2 toxicities. Four women reported lymph-oedema as a late effect. There were no radiation-related deaths reported in our population.

Toxicity rates were compared across the BMI groups according to each radiotherapy modality; EBRT and brachytherapy, EBRT or brachytherapy alone (Table 3, 4 and 5). There were no differences in the incidence of overall, acute and late toxicities between the BMI groups receiving a combination of EBRT and brachytherapy (P=0.565, P=0.645, P=0.557). Sixty-two percent of non-obese women reported a grade ≥ 2 acute toxicity versus 33.3% in obese women, although this did not significantly differ (P=0.158). The most common acute toxicities involved the lower gastro-intestinal (GI) tract and pelvis (N=16), or the genito-urinary system

Table 3 Radiation toxicities of EBRT and brachytherapy according to BMI groups

	BMI < 30 kg/m² N=35		BMI ≥ 30 kg/m² N=28		Analysis P-value
Overall toxicities					0.565
Yes	20	(57.1%)	18	(64.3%)	
No	15	(42.9%)	10	(35.7%)	
Acute toxicities					0.645
Yes	13	(37.1%)	12	(42.9%)	
No	22	(62.9%)	16	(57.1%)	
Acute toxicity grade					0.158
1	5	(38.5%)	8	(66.7%)	
≥ 2	8	(61.5%)	4	(33.3%)	
Late toxicities					0.557
Yes	13	(39.4%)	9	(32.1%)	
No	20	(60.6%)	19	(67.9%)	
Late toxicity grade					0.674
1	6	(46.2%)	3	(33.3%)	
≥ 2	7	(53.8%)	6	(66.7%)	

*: P< 0.05

(N=10), and incidences did not differ between groups (P=0.948, P=0.740). Incidence of late toxicities did not differ between groups, of which the majority comprised intestinal (P=0.597) and bladder toxicities (P=1.000, data not shown) and 59% of women had a grade 2 toxicity or higher.

There was no difference in overall toxicities, acute toxicities or late toxicities between the BMI groups in the EBRT treatment group (Table 4). The most prevalent acute toxicities of single mode EBRT were lower GI and pelvis, and genito-urinary complications, with the former being reported by four non-obese women and seven obese women (P=0.670), and genito-urinary complications by one in the non-obese group and three obese women (P=0.594). We found no significant differences between groups in terms of individual acute and late toxicities (data not shown). For brachytherapy, acute toxicities were more prevalent than late toxicities, but did not show an association with BMI (Table 5). Furthermore, individual complications did not significantly differ among groups (data not shown).

Table 4 Radiation toxicities of EBRT according to BMI groups

	BMI < 30 kg/m² N=10		BMI ≥ 30 kg/m² N=12		Analysis P-value
Overall toxicities					0.348
Yes	6	(60.0%)	10	(83.3%)	
No	4	(40.0%)	2	(16.7%)	
Acute toxicities					0.192
Yes	4	(40.0%)	9	(75.0%)	
No	6	(60.0%)	3	(25.0%)	
Acute toxicity grade					0.266
1	3	(75.0%)	3	(33.3%)	
≥ 2	1	(25.0%)	6	(66.7%)	
Late toxicities					1.000
Yes	3	(33.3%)	3	(27.3%)	
No	6	(66.7%)	8	(72.7%)	
Late toxicity grade					1.000
1	0	(0%)	0	(0%)	
≥ 2	3	(100%)	3	(100%)	

*: P< 0.05

Table 5 Radiation toxicities of brachytherapy according to BMI groups

	BMI < 30 kg/m² N=18		BMI ≥ 30 kg/m² N=7		Analysis P-value
Overall toxicities					0.637
Yes	10	(55.6%)	3	(42.9%)	
No	8	(44.4%)	4	(57.1%)	
Acute toxicities					0.362
Yes	7	(38.9%)	1	(14.3%)	
No	11	(61.1%)	6	(85.7%)	
Acute toxicity grade					1.000
1	5	(71.4%)	1	(100%)	
≥ 2	2	(28.6%)	0	(0%)	
Late toxicities					1.000
Yes	6	(33.3%)	2	(28.6%)	
No	12	(66.7%)	5	(71.4%)	
Late toxicity grade					1.000
1	4	(66.7%)	1	(50%)	
≥ 2	2	(33.3%)	1	(50%)	

*: P< 0.05

There was no significant difference in OS (P=0.467) and DFS (P=0.793) between obese and non-obese women (data not shown). In addition, recurrence rates did not differ between groups, with a rate of 17.5% in non-obese women and 14.9% in obese women (P=0.652) (Table 1).

Discussion

The majority of women diagnosed with EC are overweight or obese (10). Despite extensive evidence on the negative effect of increasing BMI on surgery and adjuvant chemotherapy, its effect on radiotherapy has somehow been neglected (13, 16). Therefore, in this study we assessed the effect of BMI on radiotherapy toxicities in EC patients.

Our study showed that BMI does not negatively impact the incidence or severity of acute and late toxicities of radiotherapy treatment for EC. Furthermore, there were no significant differences in individual acute and late complications between obese and non-obese women. In our population, obese women had a significantly poorer ECOG performance status and more comorbidities compared to the non-obese group. Despite these known patient-related risk factors for radiation toxicities, obese women did as well as their non-obese counterparts.

Our findings are supported by several studies stating that the incidence of radiotherapy toxicities is not associated with BMI (17, 18). A retrospective study (N=268) by Martra et al. showed that BMI was not significantly correlated with common acute toxicities including gastro-intestinal, genito-urinary and cutaneous toxicities after EBRT (17). Al Asiri et al. also reported no significant association between BMI and radiation toxicities. Their study reviewed 66 women receiving a combination of EBRT and brachytherapy, with a large subset of the population consisting of morbidly obese women (36.4%) (18).

In contrast, a recent study by Dandapani et al. assessing acute toxicities of 68 EC patients reported that a higher BMI was associated with increased frequency of acute grade 1 and 2 gynaecological and cutaneous toxicities (7). The authors stated that the gynaecological toxicities increase occurred with a BMI $>$ 45.2 kg/m^2. This may explain why our study did not find an association as only 5 of the 110 included women had BMI $>$ 45.2 kg/m^2. An important limitation of the study of Dandapani et al. was that it was a small study of 68 patients and heterogeneous study population comprising women receiving EBRT and/or brachytherapy. The authors did not differentiate by radiotherapy treatment received despite the known significant variation of toxicity rates among the radiotherapy modalities.

Von Gruenigen et al. retrospectively reviewed data from a randomised controlled trial of 187 patients and showed that increased BMI was significantly correlated with

less gastro-intestinal and more cutaneous toxicities after EBRT (19). However, they did not provide BMI cut-off values for clinical guidance, and as a consequence it remains unclear which BMI categories of women are at risk of more toxicities. Following these results, we have identified a clear need for future large prospective studies assessing the effect of BMI on radiotherapy toxicities and outcomes. This will also provide the opportunity to assess specific subgroups at risk such as the morbidly obese and the super obese (BMI ≥ 50 kg/m^2).

It is interesting to see that obesity does not impact radiotherapy outcomes, despite that it has been shown to significantly impact on the rate of malpositioning and size of positioning errors in EC (18, 20, 21). Lin et al. reported that an increasing BMI was found to be associated with increased setup errors and larger margin requirements, which has been confirmed by other studies in EC and other cancer sites (21-25). Authors attributed this significant association to the higher concentrations of abdominal fat causing large shifts in their tattoos because of shifting skin (21). This may force clinicians to adopt larger margins for planned target volume during EBRT planning, and suggests that specifically obese patients may benefit more from daily image guidance. A recent study showed that particularly obese women benefit from the use of field-in-field (FIF) technique compared to 3D-CRT in terms of improved dose homogeneity and dose reductions (26). In addition, in our study there was a significant difference of 3.53 Gy in mean dose received by the bowel, although this did not translate in a toxicity difference.

Survival outcomes did not significantly differ among the two BMI groups, although the study size precludes any strong conclusions. The effect of obesity on the survival of EC patients has been much debated, with studies reporting conflicting results (27, 28). A recent systematic review has stated that increased BMI is significantly associated with increased all-cause mortality, with morbidly obese women being at highest risk. The authors reported that a 10% increase in BMI resulted in a 9.2% increase in the odds of all-cause mortality (27). Moreover, we did not find an association between recurrent disease and BMI, which is in accordance with the existing literature (29).

Following that EC generally has a good prognosis with a 10-year survival of 78%, QoL is an important outcome for survivors (30). Radiotherapy has been known to negatively impact several aspects of QoL, including physical, social and role functioning as well as sexual functioning, with treatment-related symptoms persisting well into patients' survivorship years (31-34). Despite finding no significant difference in toxicity outcomes across BMI groups, it would be interesting to see whether BMI influences reported QoL impairments following radiotherapy treatment, as obesity has been shown to negatively affect the QoL of EC survivors (31, 35).

New radiotherapy techniques such as IMRT and IGRT have allowed decreased radiation exposure to structures adjacent to the clinical target regions, and may

consequently reduce treatment toxicity (36, 37). Furthermore, adaptive planning, comprising an adaptive radiotherapy plan which responds to changes in anatomy and tumour biology throughout the course of treatment, will allow clinicians to further individualise and tailor radiotherapy treatment (38, 39). However**,** reports on long-term outcomes are limited, and the impact of BMI on new techniques has yet to be assessed. Future large prospective studies are therefore needed to assess the role of BMI in order to develop specific clinical guidelines for their use in the obese population. Moreover, interventions aiming to improve toxicity complications and QoL should be encouraged, as the majority of patients will experience toxicities (3, 6). Exercise has been known to improve the QoL of cancer patients during adjuvant treatment (40, 41). It has been suggested that exercise may also improve radiation-related toxicities (42). Proposed mechanisms of a beneficial effect of exercise include an increase in endorphins and insulin-related growth factors mediating the acute radiation reaction, and possibly a systemic anti-inflammatory effect (42). Unfortunately within EC, exercise intervention studies are still in their infancy and should therefore be a focus of future investigations (43).

To our knowledge, this was the first study to date to assess the effect of BMI on toxicity rates while differentiating for different radiotherapy treatments in EC. Strengths of the study include the homogeneity of the study population and the evaluation of toxicities according to the international and validated RTOG guidelines by two clinicians (14).

Study limitations include the retrospective design and the relatively small study population. A large proportion of toxicities were grade 1 toxicities, which may be less likely to be reported. In addition, there was a variation of EBRT and brachytherapy treatment doses, although we believe this is a reflection of clinical practice and its change over time. The overall toxicity rates of EBRT and the combination EBRT and brachytherapy varied slightly, with interestingly a lower overall rate in the combination group. We believe this may be a result of the study size, even though it generally concurred with previously reported rates (3, 6, 7).

Conclusion

In this study we show that BMI does not influence the occurrence of radiation toxicities in EC. However, radiation related toxicities remain prevalent and are of particular concern for EC patients, as they may severely impact their QoL. In addition, obesity remains a challenge in the treatment of EC. Future studies need to further explore the role of obesity in radiotherapy management to provide specific clinical guidelines and assess possible interventions to improve toxicities and QoL.

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THE IMPACT OF BMI ON QUALITY OF LIFE IN OBESE ENDOMETRIAL CANCER SURVIVORS: DOES SIZE MATTER?

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Abstract

Background

Survivorship and quality of life issues are becoming increasingly relevant in endometrial cancer as a result of the marked increase in incidence of the disease combined with excellent and improving long term survival.

Objective

The purpose of this study was to evaluate the effect of obesity (BMI ≥ 30 kg/m^2) on quality of life (QoL) in endometrial cancer survivors.

Methods

Participants were endometrioid endometrial cancer survivors diagnosed between 2008 and 2013. Quality of life was measured through the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30, version 3.0). Associations between BMI and quality of life were determined by means of multivariate analyses.

Results

322 women diagnosed with endometrioid endometrial cancer were invited to participate. Excluded were 15 women with unknown BMI, 40 with non-endometrioid histology and 10 with concurrent cancer. The QLQ-C30 questionnaire was completed by 158 (61.5%) women, of which 63 women (40%) were obese (BMI ≥ 30–39.9 kg/m^2), and 30 women (19%) were morbidly obese (BMI ≥ 40 kg/m^2). Morbidly obese women reported worse physical, role and social functioning and more somatic complaints.

Conclusion

Morbid obesity is associated with poorer quality of life in endometrial cancer survivors. Lifestyle interventions such as exercise programs and diet interventions could be viable means to improve the quality of life of obese endometrial cancer survivors. Future research should focus on means to improve quality of life in obese endometrial cancer survivors.

Background

Endometrial cancer is the fourth most common cancer in the United Kingdom, accounting for 5% of all female cancers. The five year survival rate for endometrial cancer (77.3%) is among the highest of the most common cancers in England. While the incidence of several other cancers has levelled or declined in the last decades, rates for endometrial cancer have increased by over 40% since the 1990s (1). One of the main reasons for this rise is the growing obesity epidemic (2).

In 2011, 33% of adult women in England were overweight (BMI 25-29.9 kg/m^2) with a further 26% being obese (BMI of 30 kg/m^2 or greater), showing a rapid rising trend over time (2). The risk of endometrial cancer is directly related to weight increase (3–5), with higher incidence of endometrial cancer among obese women accounting for 38% up to 81% of endometrial cancer patients being obese (BMI ≥ 30 kg/m^2), and 12% to 17% being morbidly obese (BMI ≥ 40 kg/m^2) (6–9).

As the group of endometrial cancer survivors continues to grow due the rising incidence and the relatively good prognosis, there is an increasing interest in enhancing the quality of life of survivors (10). Recent studies suggest that obesity negatively impacts quality of life in early stage endometrial cancer survivors (6, 7, 11, 12). In addition, obesity is associated with higher cancer related and all-cause mortality, and disease recurrence, although this is not uniformly reported (8, 9, 13–16).

In this study we aimed to investigate the effect of obesity on quality of life in survivors of endometrioid endometrial cancer using a validated quality of life questionnaire (EORTC QLQ-C30, version 3.0).

METHODS

Study population

Women diagnosed with endometrial cancer at the Royal Cornwall Hospital (RCHT) between January 2008 and May 2013 were identified from the cancer registry of the South West Cancer Intelligence Service. Eligible women were those with endometrioid pathology who were still alive, with no history of concurrent malignancy, and in whom weight and height had been recorded at the time of diagnosis. They had been approached to participate in a departmental review of the follow up care either at their follow up appointments or by post, with an introduction letter explaining the nature of the survey. The letter was accompanied by a general questionnaire as well as a quality of life questionnaire. Consent was obtained at their review appointment or by post.

Data collection

Patient characteristics such as age at diagnosis, date of diagnosis, histology, stage, grade, treatment, and other characteristics were collected from the patients' medical records. Staging was performed through surgery using the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging, including systematic lymphadenectomy (17). Patients who did not undergo surgery (disseminated disease with poor performance status) were staged according to their radiological appearance and characteristics using the clinical staging adopted by FIGO in 1971 (18). Recurrence was defined as clinical, pathological, or radiographic evidence of disease recurrence. Information about recurrent disease was collected from the medical records of women who were included in the study, and of 35 women with endometrioid endometrial cancer who had died by the time of data collection.

The BMI (weight (kg) / [height (m)]^2) at the time of diagnosis was recorded, and categorised according to national guidelines: underweight (≤ 18.5 kg/m^2), normal range (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (≥ 30–39.9 kg/m^2) and morbidly obese (≥ 40 kg/m^2) [19]. The project was a secondary analysis of outcomes of a departmental review audit of the follow up service and therefore did not require ethical review.

Outcome measures

Quality of life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30, version 3.0). This is a validated 30-item cancer-specific questionnaire composed of both multi-item scales and single-item measures, covering several areas of quality of life; physical, emotional, cognitive, social and role functioning as well as symptoms and global quality of life. All items were rated on a 4-point scale from 1 ("not at all") to 4 ("very much"), with the exception of global health and QoL which were rated on a 6-point scale from 1 ("very poor") to 6 ("excellent") (20).

Statistical analysis

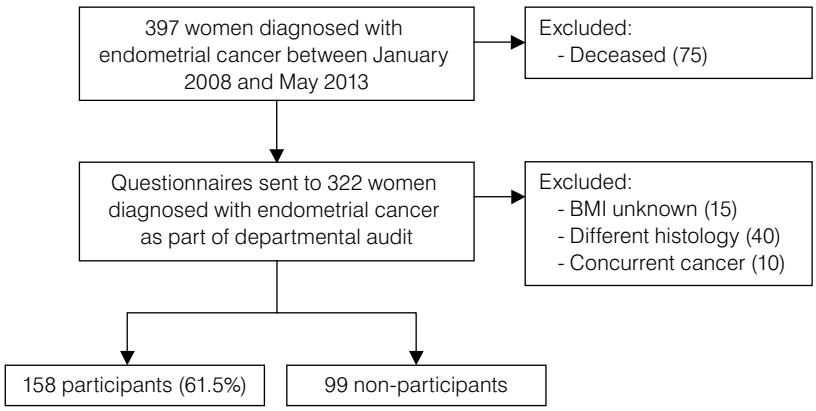
For analysis purposes, BMI data were grouped into the three categories, respectively "non-obese" (< 30 kg/m^2), "obese" (≥ 30–39.9 kg/m^2) and "morbidly obese" (≥ 40 kg/m^2) and repeated with "non-obese" combined with "obese" as one group to compare against "morbidly obese". Data were analysed with SPSS statistics version 20.0. Continuous outcomes were presented as means with standard deviations (SD), categorical outcomes were presented as frequencies and proportions. Demographic and clinical data were compared using independent samples *t*-test and one-way ANOVA for continuous data and Pearson Chi-Square for categorical variables. The EORTC QLQ-C30 outcomes were analysed according to scoring procedures and were linearly transformed into 0–100 scales. Higher scores for quality of life functional

scales and global health status represent a higher level of functioning and a high quality of life. Higher scores for symptom scales or items represent a higher level of symptomatology (21). Multivariate analyses were used to assess associations between outcome measures and BMI, while correcting for patient characteristics. P-values were regarded significant if $P<0.05$ and tests were two-sided.

Results

A total of 397 women were diagnosed with endometrial cancer at the RCHT between January 2008 and May 2013, of which 75 women were deceased at the time of the study and were therefore excluded. Consequently, 322 women diagnosed with endometrial cancer were invited to participate. Excluded from further analysis in this study were 15 women with unknown BMI, 40 women with non-endometrioid histology and 10 women with concurrent cancer. Of the remaining 257 women with endometrioid endometrial cancer, 158 (61.5%) completed the questionnaire (the participants) and 99 failed to return them (the non-participants) (Figure 1).

Figure 1 Flow chart of recruitment to the study



Baseline and clinical characteristics

The mean age of both participants and non-participants combined was 66 years (SD 9.74). The majority (94.9%) was diagnosed with early stage (I and II) endometrial cancer. Almost all women had undergone surgery (98.1%), and a small number received chemotherapy and/or radiotherapy. The median time since diagnosis was 30 months (range 2–81). There was no significant difference in the baseline and clinical characteristics between the participants in the study compared to those who failed to return the questionnaire (Table 1).

Table 1 Baseline and clinical characteristics of participants and non-participants

	Participants N=158	Non-participants N=99	Analysis P-value
Age (mean, SD)	70.0 (8.85)	64.7 (10.92)	0.076
Performance status (ECOG)			0.116
0	98 (62.0%)	47 (47.5%)	
1	30 (19.0%)	24 (24.2%)	
2	6 (3.8%)	4 (4.0%)	
3	4 (2.5%)	1 (1.0%)	
4	0 (0.0%)	1 (1.0%)	
Unknown	20 (12.7%)	22 (22.2%)	
Body mass index			0.847
Non-obese (< 30 kg/m^2)	65 (41.1%)	42 (42.4%)	
Obese (30-39.9 kg/m^2)	63 (39.9%)	41 (41.4%)	
Morbidly obese (≥ 40 kg/m^2)	30 (19.0%)	16 (16.2%)	
Stage			0.194
Early (1-2)	149 (94.3%)	95 (96%)	
Late (3-4)	7 (4.4%)	1 (1.0%)	
Unknown	2 (1.3%)	3 (3.0%)	
Grade			0.312
1	70 (44.3%)	40 (40.4%)	
2	69 (43.7%)	40 (40.4%)	
3	19 (12.0%)	18 (18.2%)	
Unknown	0 (0.0%)	1 (1.0%)	
Operation			0.945
Yes	155 (98.1%)	97 (98.0%)	
No	3 (1.9%)	2 (2.0%)	

Table 1 Continued

	Participants N=158		Non-participants N=99		Analysis P-value
Type of operation					0.220
TAH + BSO	52	(32.9%)	42	(42.4%)	
TLH + BSO	98	(62.0%)	48	(48.5%)	
LAVH + BSO	4	(2.5%)	4	(4.0%)	
Other	1	(0.6%)	3	(3.0%)	
None	3	(1.9%)	2	(2.0%)	
Chemotherapy					0.330
Yes	6	(3.8%)	2	(2.0%)	
No	152	(96.2%)	96	(97.0%)	
Unknown	0	(0.0%)	1	(1.0%)	
Radiotherapy					0.445
Yes	28	(17.7%)	18	(18.2%)	
No	130	(82.3%)	80	(80.8%)	
Unknown	0	(0.0%)	1	(1.0%)	
Time since diagnosis					0.961
< 1 year	32	(20.3%)	19	(19.2%)	
1 - < 2 years	35	(22.2%)	23	(23.2%)	
2 - < 3 years	35	(22.2%)	18	(18.2%)	
3 - < 4 years	27	(17.1%)	18	(18.2%)	
4 - < 5 years	22	(13.9%)	17	(17.2%)	
≥ 5 years	7	(4.4%)	4	(4.0%)	
Recurrence					0.559
Yes	3	(1.9%)	3	(3.0%)	
No	155	(98.1%)	96	(97.0%)	

BSO: bilateral salpingo-oophorectomy; ECOG: Eastern Cooperative Oncology Group; LAVH: laparoscopic assisted vaginal hysterectomy; SD: standard deviation; TAH: total abdominal hysterectomy; TLH: total laparoscopic hysterectomy

Table 2 compares the baseline and clinical characteristics of the 158 women who returned the questionnaire according to their BMI status. Sixty-five (41%) were non-obese (mean BMI 25.7, minimum 18), 63 (40%) were obese (mean BMI 34.3), and 30 women (19%) were morbidly obese (mean BMI 44.9, maximum 64). Non-obese women were significantly older than the obese and morbidly obese women at the time of diagnosis (P=0.042). The morbidly obese women had a significantly worse

Table 2 Baseline and clinical characteristics of participants according to BMI categories

	Non-obese (< 30 kg/m²) N=65		Obese (30-39.9 kg/m²) N=63		Morbidly obese (≥ 40 kg/m²) N=30		Analysis P-value
Age (mean, SD)	69.0 (10.05)		66.0 (8.30)		64.6 (6.12)		0.042*
Performance status							<0.001*
0	47	(72.3%)	42	(66.7%)	9	(30.0%)	
1	6	(9.2%)	16	(25.4%)	8	(26.7%)	
2	3	(4.6%)	2	(3.2%)	1	(3.3%)	
3	0	(0.0%)	0	(0.0%)	4	(13.3%)	
4	0	(0.0%)	0	(0.0%)	0	(0.0%)	
Unknown	9	(13.8%)	3	(4.8%)	8	(26.7%)	
Stage							0.035*
Early (1-2)	61	(93.8%)	60	(95.2%)	28	(93.3%)	
Late (3-4)	4	(6.2%)	3	(4.8%)	0	(0.0%)	
Unknown	0	(0.0%)	0	(0.0%)	2	(6.7%)	
Grade							0.734
1	27	(41.5%)	32	(50.8%)	11	(36.7%)	
2	30	(46.2%)	24	(38.1%)	15	(50.0%)	
3	8	(12.3%)	7	(11.1%)	4	(13.3%)	
Operation							0.085
Yes	64	(98.5%)	63	(100%)	28	(93.3%)	
No	1	(1.5%)	0	(0.0%)	2	(6.7%)	
Type of operation							0.445
TAH + BSO	22	(33.8%)	20	(31.7%)	10	(33.3%)	
TLH + BSO	41	(63.1%)	39	(61.9%)	18	(60.0%)	
LAVH + BSO	1	(1.5%)	3	(4.8%)	0	(0.0%)	
Other	0	(0.0%)	1	(1.6%)	0	(0.0%)	
None	1	(1.5%)	0	(0.0%)	2	(6.6%)	
Chemotherapy							0.481
Yes	3	(4.6%)	3	(4.8%)	0	(0.0%)	
No	62	(95.4%)	60	(95.2%)	30	(100%)	
Radiotherapy							0.064
Yes	17	(26.2%)	8	(12.7%)	3	(10.0%)	
No	48	(73.8%)	55	(87.3%)	27	(90.0%)	

Table 2 Continued

	Non-obese (< 30 kg/m²) N=65		Obese (30-39.9 kg/m²) N=63		Morbidly obese (≥ 40 kg/m²) N=30		Analysis P-value
Time since diagnosis							0.708
<1 year	12	(18.5%)	13	(20.6%)	7	(23.3%)	
1 - < 2 years	15	(23.1%)	15	(23.8%)	5	(16.7%)	
2 - < 3 years	11	(16.9%)	14	(22.2%)	10	(33.3%)	
3 - < 4 years	13	(20.0%)	12	(19.0%)	2	(6.7%)	
4 - < 5 years	11	(16.9%)	6	(9.5%)	5	(16.7%)	
≥ 5 years	3	(4.6%)	3	(4.8%)	1	(3.3%)	
Recurrence							0.361
Yes	2	(3.1%)	0	(0.0%)	1	(3.3%)	
No	63	(96.9%)	63	(100%)	29	(96.7%)	

BSO: bilateral salpingo-oophorectomy; ECOG: Eastern Cooperative Oncology Group; LAVH: laparoscopic assisted vaginal hysterectomy; SD: standard deviation; TAH: total abdominal hysterectomy; TLH: total laparoscopic hysterectomy; *: P<0.05

performance status compared to the obese and non-obese women (P<0.001). None of the morbidly obese women was diagnosed with late stage disease (P=0.035) though in two cases the stage was not known.

Quality of life

Mean scores of reported outcomes of the QLQ-C30 questionnaire in endometrial cancer survivors according to BMI categories are described in Table 3. The global quality of life of endometrial cancer survivors was highest among non-obese women, but not significantly different from obese and morbidly obese women. Outcomes of obese women did not significantly differ from non-obese women in any quality of life subscale. However, women who were morbidly obese (BMI ≥ 40 kg/m²) at time of diagnosis reported significantly worse physical functioning (P=0.002) but had similar outcomes in all other functioning scales when compared to non-obese and obese women. They also had significantly more dyspnoea (P=0.016) and diarrhoea (P=0.030) but did not differ from non-obese and obese women in other symptom distress scores.

In addition, we have compared quality of life outcomes of the morbidly obese women to the women with a BMI below 40 kg/m² (non-obese and obese groups combined). This showed a significantly worse physical, role and social functioning (P=0.001, P=0.017 and P=0.023), and significantly more dyspnoea, pain and diarrhoea (P=0.037, P=0.025 and P=0.009) in morbidly obese women (Table 3).

Table 3 Outcomes of QLQ-C30 questionnaires of participants according to BMI categories

	Non-obese		Obese		Morbidly obese		Analysis	BMI < 40 kg/m² vs. morbidly obese
	N=65		N=63		N=30			
	Mean (SD)						P-value	P-value
Global quality of life	79	(18)	75	(22)	68	(25)	0.077	NS
Functional scales								
Physical functioning	85	(17)	81	(17)	66	(29)	0.002*	0.001*
Role functioning	87	(20)	83	(26)	71	(33)	0.052	0.017*
Emotional functioning	88	(17)	83	(21)	88	(21)	0.512	NS
Cognitive functioning	91	(14)	90	(15)	81	(31)	0.513	NS
Social functioning	91	(18)	89	(21)	78	(31)	0.073	0.023*
Symptom scales								
Fatigue	20	(20)	24	(22)	31	(25)	0.071	NS
Nausea and vomiting	3	(7)	5	(10)	7	(17)	0.667	NS
Pain	13	(21)	18	(27)	26	(29)	0.086	0.025*
Dyspnoea	10	(19)	17	(22)	24	(28)	0.016*	0.037*
Insomnia	27	(28)	22	(30)	15	(19)	0.112	NS
Appetite loss	6	(14)	5	(15)	4	(12)	0.927	NS
Constipation	16	(23)	9	(19)	10	(22)	0.077	NS
Diarrhoea	3	(11)	4	(12)	9	(15)	0.030*	0.009*
Financial difficulties	5	(16)	7	(23)	6	(20)	0.917	NS

*: P-value <0.05; NS: not significant

Obesity, quality of life and stage of disease

BMI did not have a significant effect on global quality of life in women with early stage endometrial cancer. However, morbidly obese women reported significantly worse physical functioning compared to non-obese and obese women with early stage disease (P=0.007). In addition, obese and morbidly obese women experienced significantly more dyspnoea and diarrhoea than non-obese women with early stage disease (P=0.007 and P=0.013). In total, seven women were diagnosed with late stage endometrioid endometrial cancer, of which four women were non-obese and three women were obese. There were no morbidly obese women diagnosed with late stage endometrial cancer (Table 2).

Obesity and recurrence

There was no significant effect of obesity on recurrent disease in the 292 women diagnosed with endometrioid endometrial cancer (data not shown). Recurrence rates among non-obese, obese and morbidly obese women were respectively 6.6% (N=8), 2.5% (N=3) and 7.7% (N=4).

Discussion

The prognosis for women with endometrial cancer is good, with the age-standardised relative survival rates in England during 2005–2009 showing that 74.4% of women are surviving ten years or more (1). As such, survivorship and quality of life issues are very relevant to their care. Cancer survivorship entails the maintenance of physical, social, sexual, spiritual, and economic wellbeing. Assessment of factors that impact quality of life in endometrial cancer survivors is important to develop a tailored survivorship programme and excellent quality of care.

Endometrial cancer and obesity are inextricably associated with one another. Weight of endometrial cancer survivors does not seem to change over time and cancer survivors find it difficult to implement lifestyle changes (22–24). Therefore novel approaches dealing with obese endometrial cancer patients are important to help maintain a high QoL for long-term survivors.

In this study, 59% of endometrial cancer survivors had a BMI of ≥ 30 kg/m^2, and 19% were morbidly obese (BMI ≥ 40 kg/m^2), which is consistent with previously reported data (6-9). Morbidly obese women had a significantly worse performance status compared to non-obese and obese, probably because of their functional limitations and comorbidities due to their excessive weight (25, 26). Measures that improve the performance status at diagnosis including pre-operative optimisation and prehabilitation should be considered.

Previous studies have reported a significantly poorer quality of life in endometrial cancer survivors with a BMI of ≥ 30 kg/m^2, which further deteriorates as BMI increases (6, 7, 11, 12). However, our study indicates that significant quality of life deterioration is reported by morbidly obese endometrial cancer survivors but that obese women with BMI below 40 kg/m^2 do not experience poorer quality of life compared to the non-obese.

Morbidly obese women reported significantly worse physical functioning compared to non-obese and obese endometrial cancer survivors, which is in line with previous research (7, 11, 12). A recent study by Oldenburg et al. found that women with a higher BMI reported lower physical function, lower vitality and more fatigue symptoms (12). Two other studies also associated higher BMI with lower physical functioning, but found no significant effect on symptom distress (7, 11). In

our study, morbidly obese endometrial survivors experienced more dyspnoea, pain and diarrhoea when compared to non-obese and obese women combined, although this was not found in other studies (6, 7, 11, 12).

Morbidly obese women reported significantly worse social and role functioning. Other studies did not report a significant relationship between BMI and social functioning (6, 11, 12). The effect of BMI on role functioning has not been assessed by other studies due to the fact that they used different questionnaires (6, 9, 11, 12). Furthermore, morbidly obese women reported significantly more pain and diarrhoea ($P = 0.025$ and $P = 0.009$), these symptoms are known to be associated with obesity (27, 28).

How obesity affects quality of life still remains unclear. We can hypothesize that obesity affects quality of life through limited mobility, decreased physical endurance and its associated comorbidities, as well as through social discrimination (25, 27, 28). Lifestyle interventions may improve the quality of life in obese endometrial cancer survivors. There is considerable evidence that lifestyle modifications lead to improved general health and quality of life in other cancer sites such as colorectal, breast and prostate cancer (29–31). Thus far, there has only been one study that evaluated a lifestyle intervention in obese endometrial cancer survivors, stating that a lifestyle intervention programme in endometrial cancer survivors is feasible and that behaviour change and weight loss are achievable (32,33).

Strength of our study is the use of an internationally well-established and validated instrument to evaluate quality of life. Secondly, data of both participants and non-participants were presented and showed no significant differences, which increase the applicability of our results. The response rate was 61.5%, and is generally in line with response rates found in other studies (6, 7, 12). Reasons for not returning the questionnaires have not been reported. However, we were able to contact by phone five women who did not return the questionnaire, two explained that they just misplaced the forms, two claimed to have forgotten to complete the questionnaire and send it back one felt that she did not have a good experience while in the hospital but did not want to fill the questionnaire and express her dissatisfaction with the care she received by the ward staff.

In addition, measured height and weight were used to calculate BMI, which enhances the validity of our results. Weight of endometrial cancer survivors does not seem to change over time and cancer survivors find it difficult to implement lifestyle changes, therefore BMI at time of diagnose was found representable (22–24). Finally, we have assessed recurrence rates in all women diagnosed with endometrioid endometrial cancer, which improves the completeness and validity of our results.

Potential limitations of this study are the relatively small sample size and the absence of socio-demographic information, which prohibited adjustment for potential confounding by socio-demographic characteristics. In addition, other variables such

as comorbidities and sexual function that are known to influence quality of life in endometrial cancer survivors have not been assessed in this study (12, 34). Another potential limitation is the use of a generic quality of life questionnaire without the validated endometrial cancer specific QLQ-EN24 module (35). This module was not used in the previously described audit and therefore not available for this study.

Conclusion

Our study demonstrates that morbid obesity is associated with poorer quality of life in endometrial cancer survivors. Irrespective of the BMI levels at which quality of life deterioration occurs, weight loss should be recognised as an important goal for obese endometrial cancer survivors. Survivorship programmes including lifestyle interventions such as exercise programs and diet interventions could be viable means to improve the quality of life of obese endometrial cancer survivors. Studies evaluating the effects of lifestyle interventions on quality of life are needed, because all endometrial cancer survivors deserve to live to the fullest.

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4b

BMI AND QUALITY OF LIFE OUTCOMES IN ENDOMETRIAL CANCER SURVIVORS – A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background

Obesity is a risk factor for developing endometrial cancer and known to negatively affect outcomes and survival. However, the association between obesity and quality of life of endometrial cancer survivors remains unclear.

Objectives

To assess the association between body mass index (BMI) and the quality of life of endometrial cancer survivors. In addition, we assessed the associations between BMI and anxiety, depression and sexual function of endometrial cancer survivors.

Methods

The review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, and the Cochrane Handbook for Systematic Reviews of Interventions. We performed a search of Medline (1946-2014), Embase (1980-2014), Cinahl (1981-2014), and PsycInfo (1806-2014) to identify studies that reported on the association between BMI and quality of life outcomes in endometrial cancer survivors.

Results

Seven studies fulfilled the inclusion criteria, of which four studies could be included in the analysis. The four studies which included 1362 patients, showed that obese survivors had a significantly poorer physical functioning (P=0.001, MD: -11.61, 95% CI -18.66 to -4.55), social functioning (P=0.01, MD -4.37, 95% CI -7.75 to -1.00) and role functioning (P=0.002, MD -5.44 95% CI -8.90 to -1.98) when compared to non-obese women. Emotional and cognitive functioning did not show significant differences (P=0.18, P=0.21).

Conclusion

Obesity is associated with poorer quality of life outcomes in endometrial cancer survivors, including poorer physical, role and social functioning. Future research should be directed at lifestyle interventions aiming to enhance the quality of life of this group of survivors.

Background

Endometrial cancer is the most common gynaecological cancer in the United Kingdom, accounting for 5% of all female cancers with a five-year survival of 77.3% (1). As the incidence is rising, resulting in an increasing number of survivors, the interest of research has evolved beyond clinical endpoints to include the quality of life and psychological health of patients.

Obesity (body mass index (BMI) ≥ 30 kg/m^2) has been generally suggested to have an important influence on quality of life outcomes and is a major risk factor for developing endometrial cancer (2). This inextricable association has resulted in up to 81% of endometrial cancer patients being obese (3-5). In addition, women with high BMI tend to develop endometrial cancer at a younger age, resulting in a group of women for who survivorship will encompass decades (6).

We have recently evaluated the association between BMI and quality of life of endometrial cancer survivors at our institution, and found that only morbidly obese women (BMI ≥ 40 kg/m^2) had a poorer quality of life (3). In addition, obese women with a BMI < 40 kg/m^2 reported similar quality of life outcomes as non-obese survivors, contradictory to previous reports describing significant deteriorations at a BMI level of 30 kg/m^2 (3, 4, 7). Although the inverse association between BMI and quality of life seems evident, a definite BMI level at which clinically important deterioration occurs has not yet been identified nor established. In addition, the affected quality of life domains vary among studies causing the magnitude of the association to remain unclear.

A systematic review will clearly identify the BMI levels at which quality of life outcomes are affected and therefore help plan appropriate care for women at risk. In addition, we believe other outcomes influencing quality of life, such as anxiety, depression and sexual function should be taken into account (8-11). We have therefore performed a systematic review on the association between BMI and quality of life outcomes of endometrial cancer survivors.

Objectives:

- To assess the association between BMI and quality of life of endometrial cancer survivors.
- To assess the association between BMI and anxiety and depression in endometrial cancer survivors.
- To assess the association between BMI and sexual function of endometrial cancer survivors.

Methods

Criteria for considering studies for this review

This review was done according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (12), and in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions (13). Studies evaluating the association between BMI and quality of life, anxiety, depression or sexual function in endometrial cancer survivors were identified. Eligible study designs include; randomised controlled trials, controlled clinical trials, case-control studies, cross-sectional studies and cohort studies.

Types of participants

- Adult women (age ≥ 18 years) diagnosed with endometrial cancer.
- Women who have completed treatment.

Primary outcomes

Quality of life measured using a scale that has been validated through reporting of norms, such as;

- European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30)
- EORTC Endometrial cancer specific quality of life module (EORTC QLQ-EN24)
- Functional Assessment of Cancer Therapy (FACT)
- Medical Outcome Study Short Form-36 (SF-36)

Secondary outcomes

Anxiety, measured using a scale that has been validated through reporting of norms such as;

- Hospital Anxiety and Depression Scale (HADS)
- State Trait Anxiety Inventory (STAI)

Depression, measured using a scale that has been validated through reporting of norms such as;

- Hospital Anxiety and Depression Scale (HADS)
- Centre for Epidemiologic Studies - Depression Scale (CES-DS)
- Beck Depression Inventory (BDI)

Sexual function, measured using a scale that has been validated through reporting of norms, such as;

- Female Sexual Function Index (FSFI)

Search methods for identification of studies

The protocol for the systematic review was based on the PRISMA statement (12). We performed systematic searches of respectively; BMI and the primary outcome (quality of life), and BMI and secondary outcomes including anxiety, depression, and sexual function. Searches were performed in Medline (1946 until October 2014), Embase (1980 until October 2014), Cinahl (1981 until October 2014), PsycInfo (1806 until October 2014) and the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register. Search strategies were adapted accordingly to each database. The Medline, Embase, Cinahl, PsycInfo and the Cochrane Trial Register search strategies based on terms related to the review topic are presented in Appendix 1 and Appendix 2 respectively. In addition we searched abstracts of scientific meetings as well as manually checking the reference lists of eligible studies to identify any additional studies to include in the review. No other resources were utilised for the identification of studies.

Data collection and analysis

Selection of studies

Eligible studies included all studies examining original data on the association between BMI and quality of life outcomes in women treated for endometrial cancer. Two reviewers (AS and KG) independently assessed titles and abstracts of all identified studies. Those studies that clearly did not meet the inclusion criteria were excluded. Potentially relevant studies were retrieved in full text, and were further reviewed for eligibility by the reviewers. Differences were resolved by discussion on appeal to a third review author (AL). The risk of bias instrument recommended by the Cochrane Non-Randomised Studies Methods Group was used for non-randomised comparative studies (14). Additionally, the main confounders for the primary and secondary outcomes included baseline and clinical characteristics, which were identified a priori. The main confounders identified were age, performance status, time from diagnosis, treatment, recurrent disease and concurrent comorbidities.

Outcome scales of quality of life measures were transformed into scales comparable across different measures where possible (15). The social functioning scale of FACT-G was not suitable for equating to the social functioning scale of the EORTC-C30 (15). The SF-36 consisted of two role functioning scales and was therefore not used in the role functioning comparison. Cognitive functioning was only a subscale of the EORTC-C30 and was not assessed as a scale in the FACT-G or SF-36.

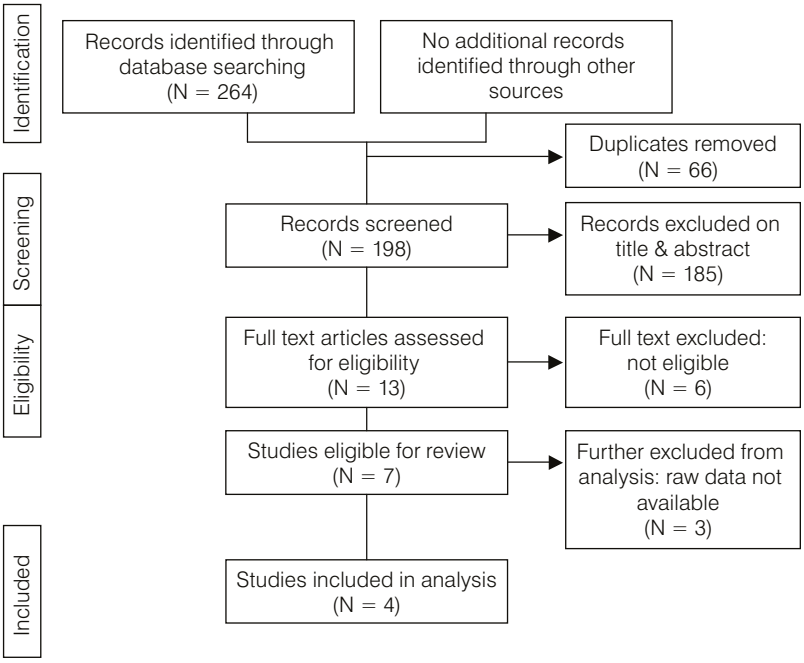
For analysis purposes, we have grouped BMI categories into respectively; ''non-obese'' (BMI < 30 kg/m^2) and ''obese'' (BMI ≥ 30 kg/m^2). In addition we created the groups; BMI < 40 kg/m^2 and ''morbidly obese'' (BMI ≥ 40 kg/m^2) for further analysis. Average weighted means and combined standard deviations were calculated for

grouped BMI categories. Raw data of the study by Smits et al. (3) was used for means and standard deviations of the grouped BMI categories. General quality of life and symptom distress scores were excluded from analysis as we found no evidence for their comparability among the different quality of life measures.

Results

The primary search strategy evaluating BMI and quality of life identified 69 references in Medline, 178 in Embase, fourteen in Cinahl and three in PsycInfo (Figure 1). Search results were merged into Endnote and duplicates were removed, resulting in 198 unique studies. After reviewing titles and abstracts, thirteen articles were retrieved in full. Full text screening further excluded six articles, resulting in seven studies being eligible for this review (Table 1).

Figure 1 PRISMA Flow diagram



The secondary search identified 198 references in Medline, 494 in Embase, 25 in Cinahl and six in PsycInfo. After removal of duplicates and review of abstracts, five articles were retrieved in full. Full text screening resulted in one eligible article evaluating the association between BMI and sexual function, which had already been selected through the primary search strategy.

Corresponding authors of three papers were contacted for additional data needed for inclusion in this review (7, 8, 16).

Included studies

In total, seven studies met the inclusion criteria, of which four studies could be included in the analysis. Characteristics of the studies are illustrated in Table 1. Two of the included studies were cross-sectional surveys (17, 18), one was a retrospective study (3) and one analysed prospectively collected data (4). All four studies combined included 1362 endometrial cancer survivors. Courneya et al. and Oldenburg et al. included only early stage (I and II) endometrial cancer survivors (17, 18), while the other two studies included all-stage survivors of which the majority (72.2% - 94.3%) had early stage disease (3, 4). BMI was categorised in different groups among the included studies, and taken at time of diagnosis or at time of completion of the questionnaires. Two studies used measured height and weight (3, 4), and the remaining studies used self-reported height and weight (17, 18). Quality of life measures used varied among studies and included the FACT-G, EORTC-C30, EORTC-EN24 and SF-36.

Body mass index and quality of life

Meta-analysis of the included studies comparing non-obese to obese endometrial cancer survivors is illustrated in Figure 2. We found a statistically significant difference in physical functioning (P=0.001), with obese survivors having poorer physical functioning (MD: -11.61, 95% CI -18.66 to -4.55). Social functioning was significantly associated with increasing BMI, with poorer outcomes in obese endometrial cancer survivors when compared to non-obese women (P=0.01, MD -4.37, 95% CI -7.75 to -1.00). In addition, role functioning was also significantly poorer in obese women (P=0.002, MD -5.44 95% CI -8.90 to -1.98), while emotional functioning and cognitive did not show a significant difference (P=0.18 and P=0.21).

Table 1 Characteristics of eligible studies

Study	Study design	Patients	BMI measure	BMI groups	Measures	Outcome
Included studies						
Nickles Fader *et al.* (4)	Prospectively collected, cross-sectional	152	Measured BMI at time of questionnaire completion	BMI ≤ 30 BMI 30-39.9 BMI ≥ 40	FACT-G SF-36	PF and RF are inversely associated with BMI
Oldenburg *et al.* (17)	Cross-sectional	666	Self-reported BMI at time of questionnaire completion	BMI < 25 BMI 25-29.9 BMI 30-24.9 BMI ≥ 35	SF-36 EORTC-EN24 FAS	PF and vitality are inversely associated with BMI
Smits *et al.* (3)	Retrospective study	158	Measured BMI at time of diagnosis	BMI < 30 BMI 30-39.9 BMI ≥ 40	EORTC-C30	Poorer PF, RF and SF in BMI ≥ 40
Courneya *et al.* (18)	Cross-sectional	386	Self-reported BMI at time of questionnaire completion	BMI < 18.5 BMI 18.5-24.9 BMI 25-29.9 BMI 30-34.9 BMI 35-39.9 BMI ≥ 40	FACT-G	PF and RF are inversely associated with BMI
Excluded studies						
Von Gruenigen *et al.* (7)	Prospective cohort study	79 ECP: 38 Benign: 41	BMI at time of diagnosis	BMI < 30 BMI ≥ 30	FACT-G SF-36	Poorer PF and PW in BMI ≥ 30
Basen-Engquist *et al.* (8)	Cross-sectional	120	Self-reported BMI at time of questionnaire completion	BMI ≤ 25 BMI 25-30 BMI > 30	SF-36 BPI BFI	PF is inversely associated with BMI
Lin *et al.* (16)	Cross-sectional	213	Self-reported BMI at time of questionnaire completion	BMI < 25 BMI 25-29.9 BMI 30-34.97 BMI 35-39.9 BMI ≥ 40	FACT-G	Overall QoL, PF and RF are inversely associated with BMI

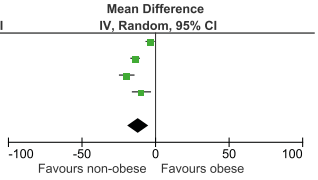
ECP: endometrial cancer patients; PF: physical functioning; PW: physical wellbeing; RF: role functioning; SF: social functioning; QoL: quality of life

Figure 2 Forest plots of comparison non-obese versus obese on quality of life outcomes

Physical functioning

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Non-obese Mean	Non-obese SD	Non-obese Total	Weight	Mean Difference IV, Random, 95% CI
Courneya 2005	80	13.3	147	83.7	14.2	239	26.5%	-3.70 [-6.50, -0.90]
Nickles Fader 2011	80	12.6	123	93.9	5	29	26.4%	-13.90 [-16.78, -11.02]
Oldenburg 2013	56.4	27.6	217	76	34.7	422	24.3%	-19.60 [-24.54, -14.66]
Smits 2014	75.8	22.8	93	85.4	16.7	65	22.8%	-9.60 [-15.76, -3.44]
Total (95% CI)			**580**			**755**	**100.0%**	**-11.61 [-18.66, -4.55]**

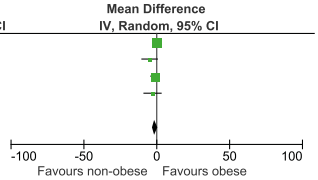
Heterogeneity: Tau² = 46.96; Chi² = 40.92, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.22 (P = 0.001)



Emotional functioning

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Non-obese Mean	Non-obese SD	Non-obese Total	Weight	Mean Difference IV, Random, 95% CI
Courneya 2005	70.6	12.7	147	70.6	12.1	239	45.1%	0.00 [-2.56, 2.56]
Nickles Fader 2011	65.7	14.7	123	70.6	12.7	29	10.7%	-4.90 [-10.20, 0.40]
Oldenburg 2013	74.8	17.8	217	76	17.5	422	35.5%	-1.20 [-4.10, 1.70]
Smits 2014	84.6	21	93	87.5	16.7	65	8.7%	-2.90 [-8.79, 2.99]
Total (95% CI)			**580**			**755**	**100.0%**	**-1.20 [-2.94, 0.54]**

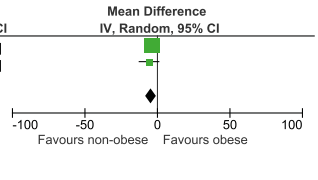
Heterogeneity: Tau² = 0.04; Chi² = 3.03, df = 3 (P = 0.39); I² = 1%
Test for overall effect: Z = 1.35 (P = 0.18)



Social functioning

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Non-obese Mean	Non-obese SD	Non-obese Total	Weight	Mean Difference IV, Random, 95% CI
Oldenburg 2013	79.6	24.2	217	83.5	23	422	75.1%	-3.90 [-7.80, -0.00]
Smits 2014	85.6	25.3	93	91.4	18.1	65	24.9%	-5.80 [-12.57, 0.97]
Total (95% CI)			**310**			**487**	**100.0%**	**-4.37 [-7.75, -1.00]**

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)



Role functioning

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Non-obese Mean	Non-obese SD	Non-obese Total	Weight	Mean Difference IV, Random, 95% CI
Courneya 2005	82.5	19.1	147	86.4	23.2	239	65.8%	-3.90 [-8.16, 0.36]
Nickles Fader 2011	77.2	19.2	123	86.4	24.2	29	13.4%	-9.20 [-18.64, 0.24]
Smits 2014	79	29	93	86.9	19.7	65	20.8%	-7.90 [-15.49, -0.31]
Total (95% CI)			**363**			**333**	**100.0%**	**-5.44 [-8.90, -1.98]**

Heterogeneity: Tau² = 0.00; Chi² = 1.51, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.08 (P = 0.002)

Cognitive functioning

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Non-obese Mean	Non-obese SD	Non-obese Total	Weight	Mean Difference IV, Random, 95% CI
Smits 2014	87.2	21.7	93	90.8	14.1	65	100.0%	-3.60 [-9.19, 1.99]
Total (95% CI)			**93**			**65**	**100.0%**	**-3.60 [-9.19, 1.99]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)

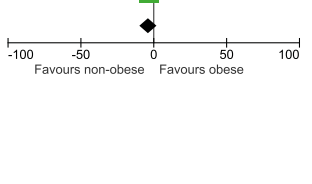
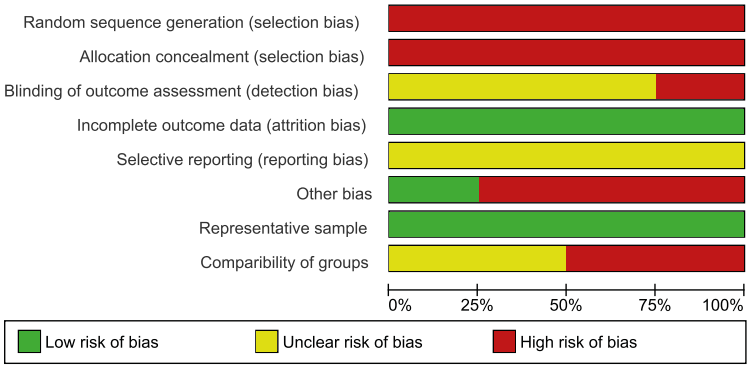
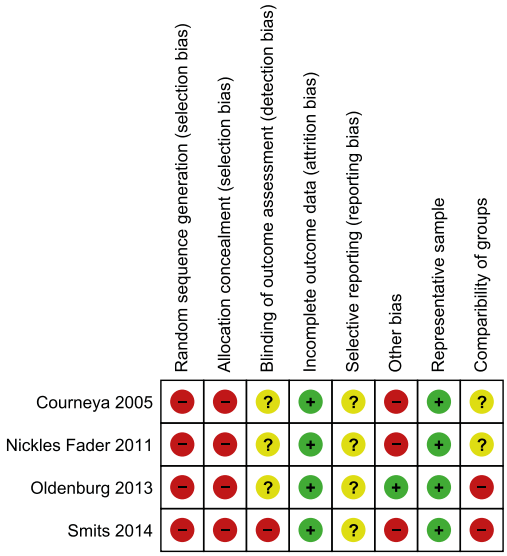


Figure 3 Risk of bias and confounding of included studies





In addition, we compared morbidly obese women to women with a BMI < 40 among studies, which showed that morbidly obese women had significantly poorer physical functioning (P=0.002, MD: -4.78, 95% CI -7.79 to -1.77), social functioning (P=0.03, MD -12.80, 95% CI -24.50 to -1.10) and role functioning (P=0.002, MD -10.03, 95% CI -16.24 to -3.82).

Body mass index and sexual function

Oldenburg et al. evaluated the association between BMI and sexual functioning through the EORTC-EN24, showing an inverse association with a higher BMI resulting in less sexual/vaginal problems. This effect persisted after adjustment for patient characteristics. However, sexual interest, sexual activity and sexual enjoyment were not associated with BMI (17).

Risk of bias and confounding

Figure 3 summarises the risk of bias and confounding for all included studies. All studies were non-randomised with a cross-sectional or retrospective design, leading to a high risk of bias associated with non-randomisation, patient attrition, and selective reporting. With regards to confounding factors, all studies reported data on a variety of possible confounders and corrected for this in their statistical analysis. Three out of the four study corrected for adjuvant treatment (chemotherapy and/or radiotherapy). However, only Oldenburg et al. adjusted for socio-demographic variables, clinical variables and comorbidities, with the other studies frequently omitting comorbidities and socio-demographic characteristics. Quality of evidence was not assessed using GRADE, as the included studies mainly comprised retrospective studies.

Discussion

To our knowledge, this is the first review to identify the evidence on the association between BMI and quality of life outcomes of endometrial cancer survivors. The results of this systematic review and meta-analysis suggest a significant deterioration in quality of life outcomes of obese survivors compared to non-obese survivors. There was a statistically significant difference in several quality of life outcomes, with obese women having poorer physical functioning, poorer social functioning and poorer role functioning when compared to non-obese women. In addition, quality of life outcomes showed a further significant deterioration in these domains when BMI increased to morbidly obese.

Thus far, the evidence has been accumulating, but failed to provide uniform guidance for clinical care. Our review provides a focus for future research and interventions to support obese women at risk of poorer quality of life during their survivorship. Unlike the results of our initial study, this review shows that significant deterioration occurs at a BMI level of 30 kg/m^2. In addition, we have identified that obesity does not just affect physical functioning but is also associated with poorer social and role functioning, contrary to the results of most individual studies (4, 7, 8, 16-18). Future interventions should also aim to improve social and role functioning, as they are significantly impaired in obese survivors.

Although it is difficult to quantify clinically important differences in quality of life scores as they vary in clinical context, minimal clinically important differences for the EORTC QLQ-C30 have been proposed by Osoba et al. and King et al. They defined a minimal difference in the EORTC scores varying from 2 to 5 (depending on domain) as clinically important, which validates the results of our meta-analysis as clinically significant (19, 20).

The influence of BMI on quality of life has received a lot of interest within endometrial cancer following its inextricable relation with obesity. As the burden of obesity on society continues to grow, the association between BMI and quality life has also been under increasing attention in other cancer sites. In breast, colorectal, bladder and prostate cancer, several studies have reported similar results of significant poorer quality of life of obese survivors, substantiating the relevance and importance of the association between obesity and poorer quality of life (21-25).

We can hypothesise that obesity negatively impacts quality of life areas through limited mobility, decreased physical endurance, associated comorbidities and social discrimination (26-28). Additionally, obesity may be associated with more treatment related symptoms and perioperative morbidities in endometrial cancer patients (29). Quality of life is paramount to women surviving endometrial cancer and our review confirms the significant role of obesity in the quality of life of survivors. The majority of endometrial cancer patients are obese and are generally diagnosed with Type 1 disease, which has a favourable prognosis with improved survival (30, 31). In addition, young obese women will be at risk of developing endometrial cancer at a pre-menopausal age, which may result in a survivor group that could face quality of life impairments for decades to come (6).

Recently, steps have been undertaken to develop novel interventions to improve patients' wellbeing after cancer treatment, frequently involving exercise and lifestyle interventions (32-36). These interventions are suggested to have a positive impact on quality of life and may influence survival outcomes as obesity has been shown to negatively influence survival (37, 38).

Completeness and applicability of evidence

We initially identified seven eligible studies for this review, of which three studies required additional data from authors. We contacted corresponding authors for each study, without any response. The majority of women included were diagnosed with early stage endometrial cancer, which is consistent with reported incidence rates (1, 39). In addition, disease stage has not been associated with poorer quality of life outcomes in gynaecological cancer survivors (40, 41).

We found one study that evaluated sexual outcomes across different BMI categories in endometrial cancer survivors through a validated subscale of EORTC-EN24 consisting of three questions. No evidence was found on the relation

between BMI and psychological outcomes such as anxiety and depression, even though this relationship has been well-established in the general population (42, 43).

Quality of evidence

The included studies had high risk of bias, largely because of their cross-sectional or retrospective designs, despite correcting for possible confounding factors. We therefore recommend that well-designed prospective studies further assess the associations between body mass index and quality of life outcomes. Furthermore, there was lack in uniformity of methods among the studies, even though all used internationally established and validated measures to evaluate quality of life (44-47). We were able to equate several of the measures according to existing evidence (15), but there may still be some discrepancy between the different measures. There is need for an assessment of the equivalence of different quality of life measures in cancer patients including the EORTC-C30, FACT-G and SF-36.

Potential biases in review process

We performed a comprehensive search of the literature, including a search of the grey literature, and data were evaluated independently by two reviewers. Unfortunately we were unable to include three studies because additional data were needed for analysis. However, all three studies showed that a higher BMI was associated with poorer quality of life outcomes, namely physical functioning and role functioning (7, 8, 16). We therefore do not expect that these data will significantly change the findings of our review.

Conclusion

Obesity is associated with poorer quality of life outcomes in endometrial cancer survivors, including poorer physical, role and social functioning. These quality of life outcomes deteriorate even further as BMI increases. Future research should be directed at lifestyle interventions aiming to enhance the quality of life of this group of survivors. In addition, we have identified a need for uniformity among quality of life measures used in the cancer population. This too needs to be addressed in future research.

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Appendix 1

Search strategy primary outcome:

1. endometrial cancer
2. endometrial neoplasm
3. endometrial carcinoma
4. uterine cancer
5. uterine neoplasm
6. uterine carcinoma
7. endometrium cancer
8. endometrium carcinoma
9. endometrium neoplasm
10. endometrioid cancer
11. endometrioid neoplasm
12. endometrioid carcinoma
13. body mass index
14. BMI
15. weight
16. (obesity OR obese)
17. quetelet* index
18. quality of life
19. life qualit*
20. ("well being" OR wellbeing)

Appendix 2

Search strategy secondary outcomes:

1. endometr* cancer
2. uter* cancer
3. endometr* neoplasm
4. uter* neoplasm
5. endometr* carcinoma
6. uter* carcinoma
7. body mass index
8. BMI
9. Weight
10. (obesity OR obese)
11. quetelet* index
12. fatigue
13. tired
14. lethargy
15. lassitude
16. pain
17. analgesia
18. fear
19. anxiet*
20. nervousness
21. psychologic* stress*
22. psychologic* distress*
23. emotional stress
24. mental suffering
25. depression*
26. ("psychologic* wellbeing" OR "psychologic* well being")
27. depress* symptom*
28. mental disorder*
29. sexual*
30. sex* disorder*
31. sex* dysfunction*
32. sex* function*
33. sex* malfunction*
34. dyspareun*

5

THE PROGNOSTIC SIGNFICANCE OF PRE-OPERATIVE BIOMARKERS IN ENDOMETRIAL CANCER: DOES BMI PLAY A ROLE?

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Submitted

Abstract

Introduction

Despite the established link between obesity and chronic inflammation, the association between body mass index (BMI), inflammatory biomarkers and their prognostic value in endometrial cancer remains unclear.

Objectives

To evaluate the prognostic value of pre-operative inflammatory biomarkers and BMI in women with endometrial cancer.

Methods

This was a retrospective cohort study of endometrial cancer patients diagnosed between January 2006 and January 2015 at the Royal Cornwall Hospital Trust. Levels of inflammatory markers including leukocytes, lymphocytes, myeloid cells, CRP, neutrophil:lymphocyte ratio (NLR) and platelet:lymphocyte ratio (PLR) were compared across BMI groups. Associations between inflammatory marker levels, BMI and overall survival (OS) were evaluated in univariate and multivariate analyses.

Results

A total of 490 women were included in the study. Obesity (BMI ≥ 30 kg/m^2) was significantly associated with higher levels of inflammatory markers, including leukocytes ($P=0.002$), lymphocytes ($P<0.001$), eosinophils ($P<0.001$), basophils ($P=0.002$), CRP ($P<0.001$), and a lower PLR ($P<0.001$) compared to non-obese women. The majority of inflammatory markers were associated with OS in univariate analyses, with higher inflammatory cell counts and higher ratios correlating to a poorer OS. After multivariate analysis, CRP ≥ 5.0 (mg/L) remained significantly associated with poorer OS ($P=0.025$).

Conclusion

Obesity is associated with inflammatory biomarkers in endometrial cancer patients. These markers are associated with prognostic factors including stage, grade and LVSI, with CRP as an independent prognostic factor for overall survival. Future studies are needed to further assess these associations, evaluating the potential usefulness of interventions targeting inflammations as a means to improve cancer outcomes.

Background

Endometrial cancer is the most common gynaecological cancer, with an incidence of around 8500 women in the United Kingdom. Over the past 20 years, incidence rates have increased by 48% (1). Obesity has been identified as one of the main contributing factors to rise in incidence, and currently affects over one third of adults in the UK (2).

Obesity causes chronic inflammation through a low-grade chronic inflammatory response in the adipose tissue. This involves multiple proinflammatory immune cell types, and is characterised by an infiltration of lymphocytes and myeloid cells including neutrophils, eosinophils and macrophages (3). It is well established that inflammation contributes to the process of carcinogenesis, and it has been proposed that obesity-related chronic inflammation plays an important role in the genesis of endometrial cancer (4, 5). Despite the established link between obesity and inflammation, few studies have assessed the association between body mass index (BMI) and inflammatory biomarkers in endometrial cancer.

Furthermore, recent studies have suggested that inflammatory response biomarkers such as leukocytes, platelet:lymphocyte ratio (PLR) neutrophil:lymphocyte ratio (NLR) and C-reactive protein (CRP) may be of prognostic value in endometrial cancer (6-8). Therefore, the possible prognostic significance of inflammatory markers in endometrial cancer needs to be further evaluated. In this study, we have investigated the prognostic value of pre-operative inflammatory biomarkers and the assocation with BMI in women with endometrial cancer.

Methods

Study population

This was a retrospective cohort study of endometrial cancer patients diagnosed between January 2006 and January 2015 at the Royal Cornwall Hospital Trust. The study population included women who received surgery for histologically confirmed primary endometrial cancer. Exclusion criteria were; i) age under 18 years at time of diagnosis, ii) an unknown preoperative BMI, iii) incomplete pre-operative full blood count results within a timeframe of 31 days prior to surgery, and iv) incomplete data on treatment course. Ethical approval was obtained through the London – Fulham Ethical committee and the study had full Trust approval.

Data collection

We identified patients through the Cancer Registry of the South West Intelligence Service which included their current status (alive versus deceased, including date of

death). Baseline and clinical characteristics were collected from patients' medical records. These included age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, medical co-morbidities, marital status and smoking status, FIGO (International Federation of Gynecology and Obstetrics) stage, grade and lympho-vascular space invasion (LVSI). BMI at time of diagnosis was calculated from recorded preoperative height and weight, and categorized into three groups; BMI $<$ 25 kg/m^2 (normal), BMI 25-29.9 kg/m^2 (overweight) or BMI $\geq$ 30 kg/m^2 (obese), respectively.

Outcomes

Full blood count data for each patient were collected within a timeframe of $<$31 days prior to surgery as part of standard clinical practice. Inflammatory markers included total white cell count (leukocytes), lymphocytes, neutrophils, eosinophils and basophils. PLR and NLR were defined as respectively; absolute platelet count divided by absolute lymphocyte count, and absolute neutrophil count divided by absolute lymphocyte count. CRP was collected within a timeframe of $<$8 weeks prior to surgery. Inflammatory markers and ratios were analysed as continuous variables and separately divided into high and low groups based on cut-off values. The cut-off values were previously defined in other endometrial cancer studies or are known clinical cut-off values; NLR 2.4, NLR 4.68, PLR 240, PLR 250, CRP 5.0 (mg/L), CRP 8.2 (mg/L), leukocytes 9000 ($10^3/\mu$l) and neutrophils 7200 ($10^3/\mu$l) (6-9). Overall survival (OS) was used for survival comparison and was defined as the time from diagnosis to death from all causes.

Statistical analysis

Data normality was assessed using Kolmogorov-Smirnov tests. Continuous data were compared using the Mann-Whitney U test, Kruskal-Wallis test or Median test, followed by post-hoc Mann Whitney U-tests. Bonferroni's correction was applied for multiple comparisons, as appropriate. Categorical data were assessed using the Pearson Chi square or Fisher's exact test. Survival analyses were performed using the Kaplan-Meier method using the log-rank test, and the Cox proportional hazards models for univariate and multivariate survival analyses. Data were analysed using IBM SPSS statistical software (10). Unknown data were excluded during the analysis. P-values of $<$0.05 were regarded as statistically significant and tests were two-sided.

Results

We identified a total of 522 women who received surgical management for histologically confirmed endometrial cancer between January 2006 and January 2015. We excluded 20 women with incomplete pre-operative blood results, nine women with incomplete data on their treatment course, and a further three with an unknown preoperative BMI. This resulted in a study population consisting of 490 patients.

Baseline and clinical characteristics of study population

The median age of the study population was 65 years (range 27-93). The majority of women (83.5%) were diagnosed with stage I disease. Ninety-five women had a of BMI < 25 kg/m^2, 143 women were overweight (BMI 25-29.9 kg/m^2) and 252 women were obese (BMI ≥ 30 kg/m^2) of which 66 were morbidly obese (BMI ≥ 40 kg/m^2). Characteristics of the study population according to BMI groups are shown in Table 1.

There were no differences between BMI groups in terms of age, ethnicity, parity, marital status and smoking status (Table 1). A higher BMI was associated with increased number of comorbidities (P=0.002) and poorer ECOG performance status (P=0.006). Significantly more obese women were diagnosed with stage I disease compared to the normal and overweight group (P=0.002), and obese women were found to have significantly less LVSI (P<0.001). Adjuvant therapy including chemotherapy (P=0.018) and radiotherapy (P=0.023) also varied significantly among BMI groups, reflecting the difference in stage.

Inflammatory markers and BMI

The values of individual inflammatory markers and NLR were available for all patients, and PLR was available for 488 women. CRP was available for 315 women as it was not routinely performed prior to 2009, after which it became part of standard pre-operative assessment as per hospital policy. However, prior to 2009, the availability of CRP was not associated with demographic or clinical characteristics (data not shown). Preoperative inflammatory markers and their associations with BMI are shown in Table 2.

A higher BMI was significantly associated with rising counts of several inflammatory markers including leukocytes (P=0.002), lymphocytes (P<0.001), eosinophils (P<0.001) and basophils (P=0.002). CRP levels were significantly higher in obese women (P<0.001). Higher BMI was also significantly associated with lower PLR ratios in obese women compared to the normal weight and overweight groups (P<0.001). No significant association was found between NLR and BMI, although there was a trend towards decreased NLR with increasing BMI (P=0.089). Furthermore, platelet counts did not significantly vary among BMI groups (P=0.754, data not shown).

Table 1 Baseline and clinical characteristics according to BMI groups

	BMI < 25 kg/m² N=95		BMI 25-29.9 kg/m² N=143		BMI ≥ 30 kg/m² N=252		Analysis P-value
Age							0.234
< 70 years	58	(61.1%)	86	(60.1%)	171	(67.9%)	
≥ 70 years	37	(38.9%)	57	(39.3%)	81	(32.1%)	
Ethnicity							0.276
White	93	(97.9%)	143	(100%)	247	(98.0%)	
Other	2	(2.1%)	0	(0%)	3	(1.2%)	
Unknown	0	(0%)	0	(0%)	2	(0.8%)	
Marital status							0.688
Married	61	(64.2%)	92	(64.3%)	159	(63.1%)	
Not married	15	(15.8%)	15	(10.5%)	40	(15.9%)	
Widowed	10	(10.5%)	18	(12.6%)	28	(11.1%)	
Unknown	9	(9.5%)	18	(12.6%)	25	(9.9%)	
Parity							0.490
None	21	(22.1%)	23	(16.1%)	45	(17.9%)	
One or more	74	(77.9%)	120	(83.9%)	207	(82.1%)	
Comorbidities							0.002*
None	29	(30.5%)	37	(25.9%)	45	(17.9%)	
One	29	(30.5%)	33	(23.1%)	49	(19.4%)	
Two or more	37	(38.9%)	72	(50.3%)	157	(62.3%)	
Unknown	0	(0%)	1	(0.7%)	1	(0.4%)	
ECOG status							0.006*
0	68	(71.6%)	88	(61.5%)	137	(54.4%)	
1	7	(7.4%)	26	(18.2%)	51	(20.2%)	
2-4	8	(8.4%)	5	(3.5%)	24	(9.5%)	
Unknown	12	(12.6%)	24	(16.8%)	40	(15.9%)	
Smoking status							0.541
Yes	10	(10.5%)	10	(7.0%)	19	(7.5%)	
No	83	(87.4%)	133	(93.0%)	233	(92.5%)	
Unknown	2	(2.1%)	0	(0%)	0	(0%)	
FIGO Stage							0.002*
I	70	(73.7%)	112	(78.3%)	227	(90.1%)	
II	9	(9.5%)	13	(9.1%)	12	(4.8%)	
III	12	(12.6%)	12	(8.4%)	8	(3.2%)	
IV	4	(4.2%)	6	(4.2%)	5	(2.0%)	
Grade							0.243
1	29	(30.5%)	48	(33.6%)	96	(38.1%)	
2	32	(33.7%)	46	(32.2%)	93	(36.9%)	
3	34	(35.8%)	47	(32.9%)	63	(25.0%)	
Unknown	0	(0%)	2	(1.4%)	0	(0%)	

Table 1 Continued

	BMI < 25 kg/m² N=95		BMI 25-29.9 kg/m² N=143		BMI ≥ 30 kg/m² N=252		Analysis P-value
Histology							0.276
Endometrioid	75	(78.9%)	108	(75.5%)	209	(82.9%)	
Non-endometrioid	17	(17.9%)	29	(20.3%)	31	(12.3%)	
Mixed	3	(3.2%)	6	(4.2%)	12	(4.8%)	
LVSI							<0.001*
Yes	33	(34.7%)	34	(23.8%)	39	(15.5%)	
No	57	(60.0%)	107	(74.8%)	211	(83.7%)	
Unknown or N/A	5	(5.3%)	2	(1.4%)	2	(0.8%)	
Cytoreduction (stage III-IV)							0.325
Complete	15	(93.8%)	15	(83.3%)	11	(84.6%)	
Optimal	1	(6.3%)	0	(0%)	0	(0%)	
Suboptimal	0	(0%)	3	(16.7%)	2	(15.4%)	
Chemotherapy							0.018*
Yes	18	(18.9%)	20	(14.0%)	21	(8.3%)	
No	77	(81.1%)	123	(86.0%)	231	(91.7%)	
Radiotherapy							0.023*
Yes	33	(34.7%)	38	(26.6%)	52	(20.6%)	
No	62	(65.3%)	105	(73.4%)	200	(79.4%)	

*: P-value <0.05

Table 2 Inflammatory markers and their associations with BMI

	BMI < 25 kg/m²		BMI 25-29.9 kg/m²		BMI ≥ 30 kg/m²		Analysis
	Median (range)						P-value
Leukocytes	7.0	(4.2-22.5)	7.3	(2.7-33.5)	7.7	(3.5-16.5)	0.002*
Lymphocytes	1.73	(0.78-3.67)	1.80	(0.64-3.72)	2.11	(0.74-5.84)	<0.001*
Neutrophils	4.59	(2.33-19.33)	4.66	(1.04-30.19)	4.93	(0.56-12.38)	0.128
Eosinophils	0.10	(0.02-0.41)	0.12	(0.02-1.40)	0.17	(0-0.83)	<0.001*
Basophils	0.04	(0-0.10)	0.04	(0-0.24)	0.05	(0-0.23)	0.002*
NLR	2.51	(1.24-11.15)	2.46	(0.71-20.37)	2.30	(0.34-8.84)	0.089
PLR	172.7	(73.6-510.8)	167.9	(54.9-588.5)	139.4	(43.8-656.8)	<0.001*
CRP	1.2	(0.1-99.0)	2.3	(0.2-58.0)	4.9	(0.2-87.0)	<0.001*

*: P-value <0.05

When separately assessing the morbidly obese (BMI ≥ 40 kg/m^2), analyses showed that CRP, (P<0.001), leukocytes (P<0.001), lymphocytes (P=0.001), neutrophils (P=0.003) and eosinophils (P=0.013) were significantly higher in morbidly obese women compared to BMI 30-39.9 kg/m^2. Furthermore, PLR was found to be significantly lower (P=0.001) in women with BMI ≥ 40 kg/m^2. NLR did not vary significantly among the obese groups (0.901).

Inflammatory markers and prognostic variables

We assessed the relation between inflammatory markers and prognostic variables, which showed that advanced stage disease (III/IV) was associated with higher levels of NLR (P<0.001), PLR (P<0.001), CRP (P=0.025) and neutrophils (P=0.009). In addition, the presence of LVSI was associated with both a higher NLR (P=0.003) and PLR (P<0.001). A higher histological grade was associated with elevated PLR (P=0.034), and lower lymphocyte counts (P=0.036). Elevated NLR (P=0.048), CRP (P=0.011) and leukocyte counts (P=0.025) were also associated with a poorer ECOG performance status. In addition, elevated CRP (P=0.007), leukocytes (P<0.001), lymphocytes (P=0.003), neutrophils (P=0.005), eosinophils (P=0.002) and basophils (P=0.010) were proportionally correlated with the number of comorbidities, and PLR was inversely correlated with comorbidities (P=0.012). None of the inflammatory markers were associated with age.

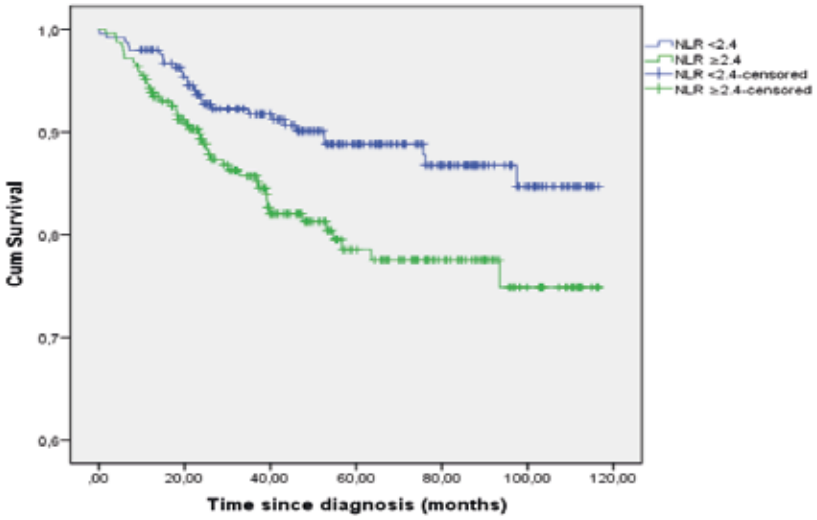
The inflammatory profile associated with obesity (BMI ≥ 30 kg/m^2) consisting of increased leukocytes, lymphocytes, eosinophils, basophils and CRP, and a decreased PLR, corresponded generally with both the favourable histopathological characteristics (stage and LVSI) and the associated ECOG performance status and comorbidities. We therefore performed an additional analysis of only women with stage 1, low grade endometrioid endometrial cancer (N=145), which showed that obese women had significantly increased inflammatory markers including WCC (P=0.039), lymphocytes (P=0.042), eosinophils (P=0.003), basophils (P=0.044), and CRP (P<0.001), and a significantly lower PLR (P=0.003) compared to non-obese women.

Inflammatory markers and survival

The median OS of the study population was 50 months (range 0-116), with a 1-year and 5-year OS of 95.8% and 74.9% respectively. Inflammatory markers including leukocyte count (P=0.001), neutrophil count (P<0.001), NLR (P=0.008), PLR (P=0.019) and CRP (P<0.001) were significantly associated with OS. Lymphocytes (P=0.458), eosinophil counts (P=0.876) and basophil counts (P=0.933) did not show an association.

Figure 1 Forest plots of comparison non-obese versus obese on quality of life outcomes

NLR cut-off value 2.4



NLR cut-off value 2.7

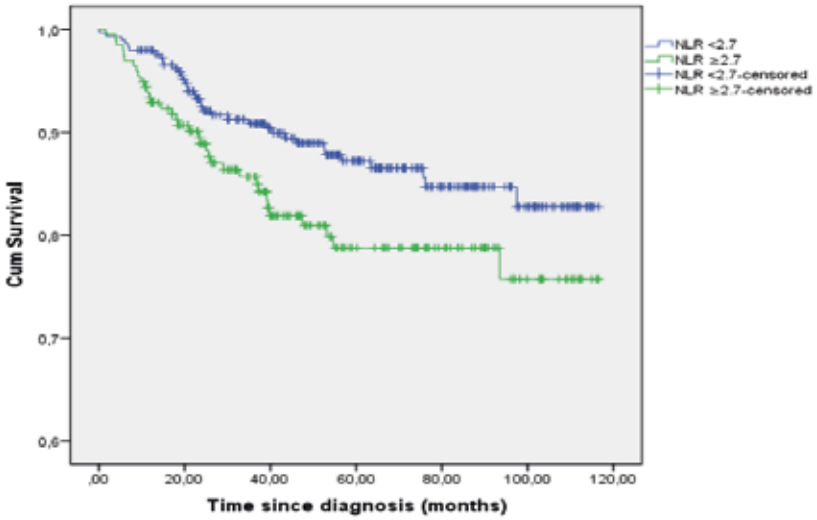
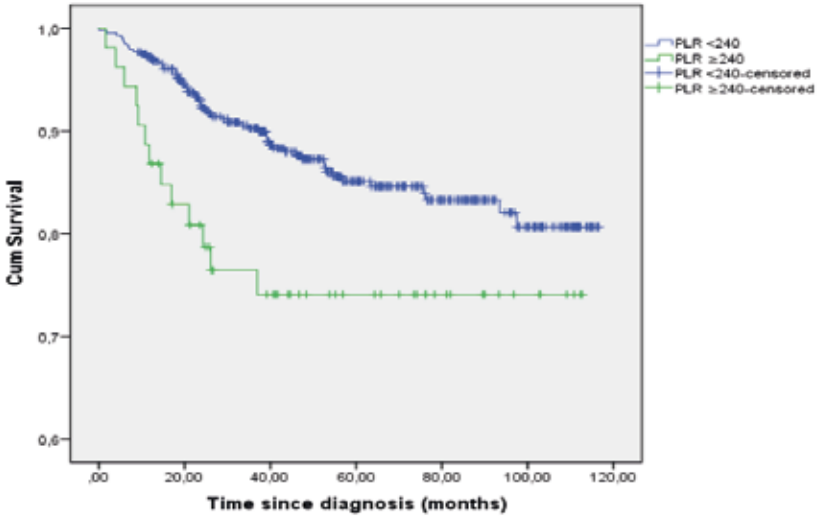


Figure 1 Continued

PLR cut-off value 240



PLR cut-off value 250

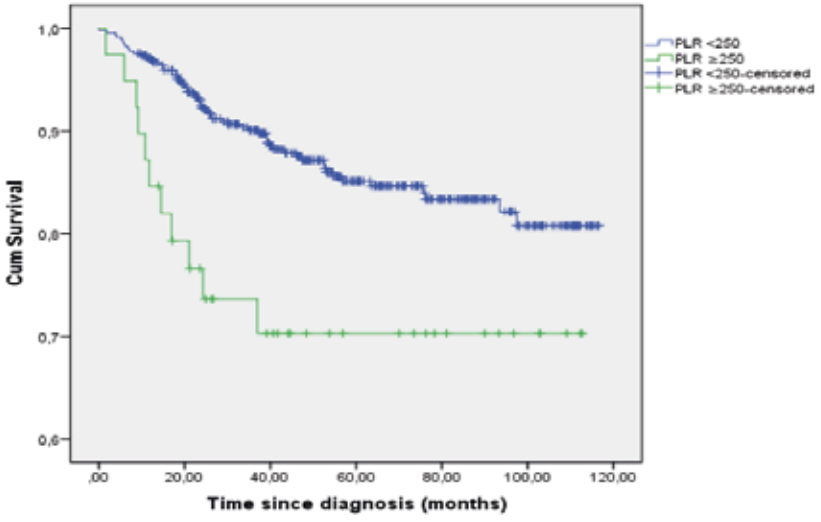
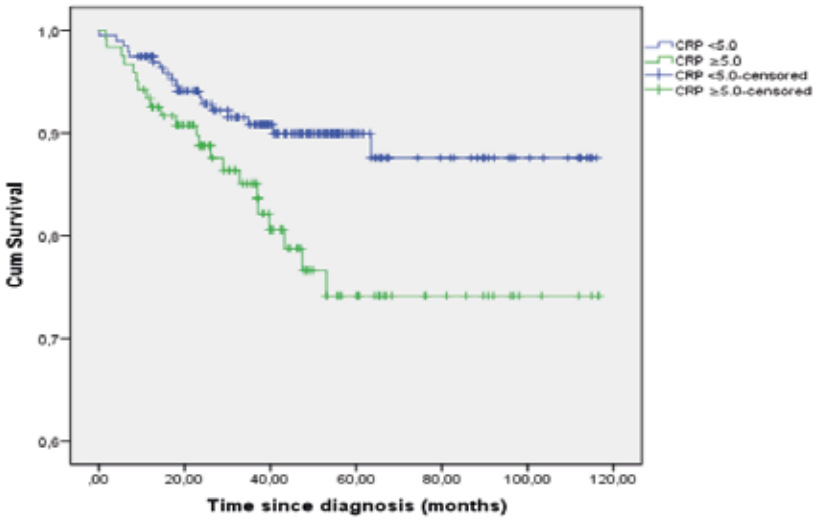


Figure 1 Continued

CRP cut-off value 5.0 (mg/L)



The predefined cut-off values NLR 2.4, NLR 2.7 PLR 240, PLR 250, CRP 5.0 (mg/L) showed a significant association with OS (Figure 1). Values of NLR ≥ 2.4 (P=0.009), NLR ≥ 2.7 (P=0.039), PLR ≥ 240 (P=0.021), PLR ≥ 250 (P=0.007) and CRP ≥ 5.0 (mg/L) (P=0.015) were associated with poorer OS (Table 3). Other cut-off values did not show significant differences in OS. After multivariate analysis, only the CRP cut-off value of 5.0 (mg/L) remained significantly associated with OS (P=0.024) (Table 3). Furthermore, we did not find a significant difference in OS between the BMI groups (P=0.886).

Table 3 Inflammatory markers cut-off values and overall survival

	Univariate analysis		**Multivariate analysis[1]**	
	Hazard ratio (CI)	**P-value**	Hazard ratio (CI)	**P-value**
NLR				
< 2.4	Referent		Referent	
≥ 2.4	1.894 (1.172-3.062)	0.009*	1.275 (0.757-2.148)	0.361
NLR				
< 2.7	Referent		Referent	
≥ 2.7	1.635 (1.026-2.605)	0.039*	1.052 (0.627-1.765)	0.849
NLR				
< 4.68	Referent		N/A	N/A
≥ 4.68	1.299 (0.595-2.837)	0.512		
PLR				
< 174	Referent		N/A	N/A
≥ 174	1.354 (0.834-2.174)	0.209		
PLR				
< 240	Referent		Referent	
≥ 240	2.029 (1.112-3.703)	0.021*	1.341 (0.698-2.579)	0.379
PLR				
< 250	Referent		Referent	
≥ 250	2.424 (1.274-4.611)	0.007*	1.413 (0.688-2.904)	0.347
CRP (mg/L)				
< 5.0	Referent		Referent	
≥ 5.0	2.176 (1.166-4.061)	0.015*	2.188 (1.103-4.340)	0.025*
CRP (mg/L)				
< 8.2	Referent		N/A	N/A
≥ 8.2	1.822 (0.959-3.459)	0.067		
Leukocytes ($10^3/\mu l$)				
< 9.0	Referent		N/A	N/A
≥ 9.0	1.499 (0.912-2.464)	0.111		
Neutrophils ($10^3/\mu l$)				
< 7.2	Referent		N/A	N/A
≥ 7.2	1.635 (0.878-3.043)	0.121		

1: Corrected for age, stage, grade and LVSI; *: P-value < 0.05; NA: not applicable; NS: not significant

Discussion

Obesity is an important risk factor for endometrial cancer, and obesity-related chronic inflammation has been suggested to contribute to carcinogenesis (4, 5). However the role of this chronic inflammation in the development of endometrial cancer is still poorly understood. This study investigated the association between pre-operative inflammatory biomarkers and BMI in endometrial cancer patients, and the prognostic value of inflammatory biomarkers in endometrial cancer.

We found that BMI is significantly associated with levels of inflammatory markers, with elevated counts of leukocytes, lymphocytes, myeloid cells and CRP, and a decreased PLR in obese women in comparison to normal and overweight women. This is the first study to extensively assess the relation between BMI and different inflammatory markers within endometrial cancer. Previous studies have only reported on CRP, stating that elevated CRP levels are associated with an increased risk of endometrial cancer and that these elevated levels correlate with increasing BMI (11, 12).

In our study, inflammatory markers were associated with prognostic variables such as stage, grade and LVSI, with advanced stage disease being associated with higher levels of NLR, PLR, CRP and neutrophils, a higher grade correlating with elevated PLR, and LVSI being associated with higher NLR and PLR. This supports growing evidence relating inflammatory markers to clinic-pathological characteristics in endometrial cancer. A recent study by Li et al. showed that high PLR, NLR and CRP are associated with advanced stage disease and non-endometrioid histology. The authors also found elevated CRP to be associated with higher grade of disease (7). Concurrently, others have reported that both high PLR and NLR correlated with a higher stage of disease and LVSI, and that increased NLR was associated with non-endometrioid histology (8, 9). However, significant associations between NLR, PLR and higher grade were not uniformly reported in these studies (7-9). A further study has identified neutrophilia (≥ 7200 10^3/ml) as a significant predictor of advanced stage and LVSI, and leukocytosis (≥ 9000 10^3/ml) as a predictor of advanced stage disease (6).

The majority of inflammatory markers were associated with OS, with higher inflammatory cell counts and higher ratios correlating to a poorer OS. However, we only identified CRP as an independent prognostic variable after multivariate analysis, mirroring findings of previous studies (6, 7, 13). Contradictory to our findings, two studies have reported NLR and PLR as independent prognostic values for overall survival (8, 9). Moreover, in other cancer sites the prognostic value of both NLR and PLR is well supported (14, 15). The difference in findings between studies may be partly attributable to the variance in cut-off values used and the fact that the majority modelled their values based on their own population. In addition, our study was comprised of a predominantly Caucasian population, while three other studies

assessed Asian populations (6, 7, 9). Further studies should determine optimal cut-off values, which are applicable to the general endometrial cancer population.

The influence of BMI on survival of endometrial cancer patients has been much debated (16). Despite a strong association between inflammatory markers and BMI, confirming the pro-inflammatory milieu in obese endometrial cancer patients, we found no significant association between BMI and OS. We did however, show that the inflammatory profile of obese women was linked to the prognostically favourable histopathological tumour characteristics, including early stage disease without LVSI, while advanced stage disease (III/IV) was associated with higher levels of NLR and PLR (17-19). This may explain the similar survival outcomes among BMI groups, another possibility for the lack of survival differences between BMI groups is the length of follow-up. As the majority of obese women diagnosed have a favourable prognosis, it is possible that significant differences will only become apparent over a longer period of time. However, differences in long-term survival may establish themselves through inflammatory-driven comorbidities associated with obesity, as they can surpass the risk of mortality from endometrial cancer (20-22).

Several inflammatory markers have been shown to be prognostic factors, and it is therefore important to assess whether these are modifiable factors. It is well established that both exercise and caloric restrictions have an anti-inflammatory effect, and that they may reduce the risk of several cancers including endometrial cancer (23-26). Studies in breast and colon cancer have shown that exercise may improve overall and disease specific survival (27). However, in endometrial cancer, lifestyle intervention studies are still in their infancy, and the role of inflammation has yet to be explored. Furthermore, anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDS) have been suggested to be protective for obesity-associated carcinogenesis, although data remains tentative (28).

Strengths of our study include the study size and validation of cut-off values defined by other studies. Our study is the first to evaluate BMI and inflammatory markers within the endometrial cancer setting, and we assessed a large range of inflammatory markers. Moreover, we corrected for variables known to influence survival to establish the independent value of the different inflammatory markers including age, stage, grade and LVSI. We did not include adjuvant therapies as a confounder as these are inherent to stage and grade of disease. The main limitations of the study are inherent to its retrospective design, which include possible selection bias and completeness of previously recorded data. Measurement of CRP prior to surgery was implemented since 2009 as routine practice, which may suggest a possible bias prior to 2009.

Future studies are needed to further assess the association between inflammatory biomarkers and obesity, especially within obesity-related cancers such as endometrial cancer. Ideally this should also include other markers such as cytokines interleukin 1

and 6 (IL-1 and IL-6) and tumour necrosis factor-α (TNF-α), which have been suggested to play an important role in inflammation and obesity (3, 5). Smith et al. recently indicated that an abundance of IL-6 and/or TNF-α produced locally by the tumour may identify a subset of endometrial cancer patients at greatest risk for treatment failure (29). However, current evidence remains limited. Furthermore, the prognostic value of inflammatory markers requires further evaluation and validation, to establish relevant cut-off values to identify women with worse prognosis. These women may be offered lifestyle counselling, and referrals to nutritionist, weight loss programmes or bariatric specialists where appropriate. Finally, we would like to recommend future lifestyle intervention studies to include an evaluation of the effect on inflammatory markers, as there is a clear need to define the role of inflammation within cancer outcomes such as survival.

Conclusion

This study shows that obesity is associated with inflammatory biomarkers in endometrial cancer patients. Several inflammatory markers are associated with prognostic factors such as stage, grade and LVSI, and we have identified CRP as an independent prognostic factor for overall survival. Future studies are needed to further assess the association between BMI and inflammatory markers, and determine its exact role in the pathogenesis and prognosis of endometrial cancer. In addition, further studies are required to establish relevant cut-off values of inflammatory markers, and to assess the potential usefulness of interventions targeting inflammations as a means to improve cancer outcomes.

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Ovarian cancer


Father Bob
PZ39
PZ620
PZ631

6

BMI AND SURGICAL OUTCOMES IN OVARIAN CANCER PATIENTS – THE ROLE OF OBESITY

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Abstract

Objectives
To evaluate the effect of body mass index (BMI) on the surgical outcomes of ovarian cancer patients. In addition, we performed a systematic review to compare our outcomes to the current literature.

Design
Retrospective cohort study and a systematic review of the literature.

Setting
Gynaecology department at the Royal Cornwall Hospital Trust.

Population
Surgically managed stage I-IV ovarian cancer patients between September 2006 and September 2014.

Methods
Primary and secondary outcome measures were evaluated across BMI categories; BMI <25 kg/m^2, BMI 25-29.9 kg/m^2, BMI ≥ 30 kg/m^2 and BMI ≥ 40 kg/m^2. A systematic review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Main outcome measures
The primary outcome measure was surgical complications. Secondary outcome measures were other intra- and post-operative outcomes.

Results
In total, 228 women were included in the study, of which 84 women had a BMI <25 kg/m^2, 84 women had a BMI 25-29.9 kg/m^2, and 60 women were obese (BMI ≥ 30 kg/m^2), of which 13 were morbidly obese. Morbid obesity was associated with increased rates of wound complications. However, BMI did not show an association with other outcomes. In the review, an increasing BMI was associated with increased rates of wound complications and hospital stay, but did not impact other surgical outcomes.

Conclusion
Obesity is associated increased rates of wound complications and a prolonged hospital stay, but does not appear to affect other operative outcomes including cytoreduction status and 30-day mortality. Therefore, operative management and post-operative care require a multifactorial approach to minimise adverse outcomes.

Background

Ovarian cancer is the seventh most common cancer in women worldwide, with nearly 239.000 new cases diagnosed in 2012 (1). Surgical management is important for both staging and treatment of ovarian cancer. Surgery is usually extensive with the aim of removing all visible disease (complete cytoreduction), as this is an important prognostic factor for survival (2).

Obesity affects more than one third of women in the United Kingdom, which is reflected in the current ovarian cancer population (3, 4). Obese patients undergoing surgery are considered to be at increased surgical risks compared to their normal weight counterparts (5). In addition, obese patients are more likely to have comorbidities that may significantly increase risk of surgical and anaesthetic morbidity and mortality (6, 7). However, the influence of obesity on surgical morbidity and outcomes in ovarian cancer has not yet been clearly defined. Kumar et al. recently identified a BMI ≥40 kg/m^2 as a possible independent prognostic factor of severe surgical morbidity and mortality, but other reports have failed to show an association between BMI and surgical morbidity and outcomes (8, 9). It is therefore important to establish whether BMI is a clinically relevant factor in predicting short-term surgical morbidity and mortality in ovarian cancer.

We therefore embarked on assessing the effect of body mass index on surgical morbidity and other surgical outcomes in ovarian cancer patients at our institution. In addition, we performed a systematic review to compare our results to the current literature.

Methods

Institutional study

Study population

We performed a retrospective study of surgically managed ovarian cancer patients between September 2006 and September 2014 at the Royal Cornwall Hospital Trust (RCHT). We included women who were diagnosed with primary ovarian cancer (including fallopian tube and primary peritoneal cancer) who had undergone surgery as part of their treatment. Exclusion criteria were an unknown BMI at time of diagnosis, and age under 18 years**.** Ethical approval was obtained through the Northampton Ethics committee and the study had full hospital approval.

Data collection

Baseline and clinical characteristics were retrieved retrospectively from patients' medical records. Body mass index (weight (kg)/[height (m)]^2) at time of diagnosis was categorised according to national guidelines, respectively; underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) obese category I (30-34.9 kg/m^2), obese category II (35-39.9 kg/m^2) and category III (morbidly obese; ≥40 kg/m^2) (6).

Outcomes

Operative morbidity was graded according to the Clavien-Dindo classification (10), and assessed as individual complications for the meta-analysis. In addition, we assessed intra- and post-operative outcomes including estimated blood loss (EBL), debulking status (complete cytoreduction: no macroscopic visible disease, optimal cytoreduction: <1 cm visible disease, or suboptimal cytoreduction: ≥1 cm visible disease), blood transfusion requirements, length of hospital stay, 30-day readmission, 30-day and 90-day mortality. Outcomes were compared according to grouped BMI categories; BMI <25 kg/m^2, BMI 25-29.9 kg/m^2, BMI ≥30 kg/m^2 and BMI ≥40 kg/m^2 respectively.

Statistical analysis

Data were analysed with SPSS statistics version 20.0 (11). Patient characteristics and outcomes were compared across the BMI categories, using nonparametric tests for continuous data, and Pearson's Chi-Square and Fisher's exact test for categorical variables. P-values were regarded significant if $P<0.05$ and tests were two-sided.

Systematic review and meta-analysis

Search strategy and selection criteria

This review was carried out according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (12), and in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions (13). Eligible for inclusion were studies evaluating the primary association between BMI and surgical morbidity and outcomes in ovarian cancer patients. Eligible study designs included; randomised controlled trials, controlled clinical trials, case-control studies, cross-sectional studies and cohort studies.

Participants; adult women undergoing surgery for all stage ovarian cancer.
Primary outcome; surgical morbidity in terms of complications.
Secondary outcomes: intra-operative outcomes including operation time, EBL, debulking status (complete, optimal and suboptimal), post-operative outcomes including hospital stay, blood transfusion rates, 30-day and 90-day mortality.

The protocol for the systematic review was based on the PRISMA statement (12). We performed systematic searches in Medline (1946 until December 2014), Embase (1980 until December 2014), and the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register. Search strategies were adapted accordingly to each database (Appendix S1).

Data collection and analysis

Selection of studies

Two reviewers (KG and AS) independently assessed titles and abstracts of studies identified. Potentially relevant studies were retrieved in full text, and were further reviewed for eligibility by both reviewers. The risk of bias instrument recommended by the Cochrane Non-Randomised Studies Methods Group was used for non-randomised comparative studies (14). Additionally, the main confounders included baseline and clinical characteristics, which were identified a priori. The main confounders identified were age, performance status, ASA (American Society of Anesthesiologists) status, disease stage, tumour involvement, and type and extent of surgery.

For analysis purposes, BMI was grouped into ''non-obese'' (BMI <30 kg/m^2) and ''obese'' (BMI ≥ 30 kg/m^2). Additionally, we compared women with a BMI <25 kg/m^2 (''normal'') to overweight / obese (BMI ≥ 25 kg/m^2, including morbidly obese) and to morbidly obese (BMI ≥ 40 kg/m^2). Dichotomous outcomes of BMI categories were combined, and for continuous outcomes average weighted means and combined standard deviations were calculated. Asian WHO defined BMI categories were combined with the corresponding international WHO defined BMI categories (15).

Results

Primary study

We identified 264 women who received surgical treatment for ovarian cancer between September 2006 and September 2014. Thirty-six women were excluded of which 12 women had an unknown BMI at time of diagnosis, 23 women had incomplete information regarding their surgical treatment and outcomes, and one woman was <18 years. This resulted in the inclusion of 228 women of which 84 women had a BMI <25 kg/m^2, 84 women were overweight (BMI 25-29.9 kg/m^2) and 60 women were obese (BMI ≥ 30 kg/m^2).

There were no differences between the BMI categories in baseline and clinical characteristics including age, ethnicity ($P=0.196$), marital and smoking status ($P=0.526$, $P=0.938$), performance status (ECOG) and FIGO stage among the BMI groups (Table 1). More obese women were ASA grade 3 compared to the other

Table 1 Baseline and clinical characteristics according to BMI categories

	BMI <25 kg/m² N=84		BMI 25-29.9 kg/m² N=84		BMI ≥30 kg/m² N=60		Analysis P-value
Age (median, range)	63.1 (21-88)		65.6 (28-85)		64.6 (19-81)		0.437
Performance status							0.207
0	56	(66.7%)	55	(65.5%)	30	(50.0%)	
1	14	(16.7%)	11	(13.1%)	16	(26.7%)	
2-4	3	(3.6%)	4	(4.8%)	6	(10.0%)	
Unknown	11	(13.1%)	14	(16.7%)	8	(13.3%)	
Comorbidities							0.033*
None	31	(36.9%)	27	(32.1%)	12	(20.0%)	
One	31	(36.9%)	28	(33.3%)	17	(28.3%)	
Two or more	22	(26.2%)	29	(34.5%)	31	(51.7%)	
ASA grade							<0.001*
1	22	(26.2%)	16	(19.0%)	1	(1.7%)	
2	46	(54.8%)	45	(53.6%)	32	(53.3%)	
3	12	(14.3%)	16	(19.0%)	22	(36.7%)	
Unknown	4	(4.8%)	7	(8.3%)	5	(8.3%)	
FIGO stage							0.177
1	24	(28.6%)	21	(25.0%)	17	(28.3%)	
2	6	(7.1%)	5	(6.0%)	10	(16.7%)	
3	46	(54.8%)	44	(52.4%)	22	(36.7%)	
4	8	(9.5%)	13	(15.5%)	10	(16.7%)	
Unknown	0	(0.0%)	1	(1.2%)	1	(1.7%)	
Chemotherapy							0.105
Yes	69	(82.1%)	71	(84.5%)	47	(78.3%)	
Neo-adjuvant	19	(22.6%)	32	(38.1%)	12	(20.0%)	
Adjuvant	50	(59.5%)	39	(46.4%)	35	(58.3%)	
No	15	(17.9%)	13	(15.5%)	13	(21.7%)	

*: P-value < 0.05; ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics

groups (P<0.001). In addition, obese women had significantly more comorbidities (P=0.033) including diabetes (P=0.020), with 11.7% of women in the BMI ≥30 kg/m² group versus 3.6% and 1.2% in the BMI <25 kg/m² and BMI 25-29.9 kg/m² group

respectively. The majority of women (82%) received chemotherapy as part of their treatment, of which 54% adjuvant and 28% neo-adjuvant chemotherapy.

Complications did not vary significantly among the different BMI groups as is shown in Table 2. Rates of complete and optimal cytoreduction were similar among groups (p=0.635), and estimated blood loss increased with higher BMI, although not significantly (P=0.271). For women with stage III-IV disease, rates of complete and optimal cytoreduction were 57% and 78% respectively, and did not vary among the BMI categories (data not shown). Other post-operative outcomes including transfusion rates, hospital stay and readmission rates were similar across the BMI groups of all patients. Overall 30-day and 90-day mortality were 3.1% and 4.8% respectively. The BMI <25 kg/m^2 group had relatively higher mortality rates but this did not vary significantly (30-day mortality; P=0.071, 90-day mortality; P=0.215).

An additional analysis of the morbidly obese women (BMI $\geq$40 kg/m^2) as a separate group (N=13) compared to the other BMI categories revealed a significantly higher incidence of wound complications in the morbidly obese group (P=0.027), with two women experiencing a wound complication (15.4%). However, there were no other significant differences in terms of operative complications, and intra- and post-operative outcomes (data not shown).

Systematic review and meta-analysis

The search strategy evaluating BMI, surgical morbidity and secondary outcomes identified 602 references, which after removal of duplicates resulted in 435 unique studies (Figure S1). After screening titles and abstracts, 42 articles were retrieved in full and were further assessed for eligibility. This resulted in five studies being eligible for this review.

We contacted the corresponding authors of three papers for additional data on separate BMI categories needed for comparisons in this review. A search of grey literature further identified four studies, but after full text screening none were eligible for this review.

Included studies

In total, six studies including our study were included in the review, and characteristics of the studies are illustrated in Table 3. Five of the six studies were retrospective studies (8, 16-18) and one used prospectively collected data (9). All studies combined resulted in a total of 2072 ovarian cancer patients. Three studies included all stage ovarian cancer (9, 17), the other studies included disease stages varying from stage II-IV to IIIc-IV (8, 16, 18). Stage was not associated with BMI in any of the studies. BMI was categorised in different groups among the studies, and Suh et al. used Asian BMI categories recommended by WHO (15). Surgical radicality in terms of complexity, extent and debulking status was assessed in the majority of studies. Kumar et al.

Table 2 Intra- and post-operative outcomes according to BMI categories

	BMI <25 kg/m² N=84		BMI 25-29.9 kg/m² N=84		BMI ≥30 kg/m² N=60		Analysis P-value
Surgical morbidity							
Complications							0.674
None	58	(71.6%)	57	(67.9%)	38	(64.4%)	
Clavien-Dindo 1+2	20	(27.7%)	23	(27.4%)	17	(28.8%)	
Clavien-Dindo 3+4	3	(3.7%)	4	(4.8%)	4	(6.8%)	
Individual complications for meta-analysis*							
Wound	0	(0%)	0	(0%)	2	(3.3%)	0.068
Ileus	12	(14.3%)	9	(10.7%)	4	(6.7%)	0.392
VTE	0	(0%)	1	(1.2%)	0	(0%)	1.000
Infection/sepsis	9	(10.7%)	11	(13.1%)	13	(21.7%)	0.166
Pneumonia	3	(3.6%)	2	(2.4%)	3	(5.0%)	0.751
Return to OR	1	(1.2%)	1	(1.2%)	1	(1.7%)	1.000
Organ failure	3	(3.6%)	1	(1.2%)	2	(3.3%)	0.664
Intra-operative outcomes							
Residual disease (stage II-IV)							0.635
No residual disease	33	(55.0%)	39	(62.9%)	28	(66.7%)	
Residual disease	27	(45.0%)	23	(37.1%)	14	(33.3%)	
Optimal (< 1 cm)	11	(18.3%)	11	(17.7%)	8	(19.0%)	
Suboptimal (≥ 1 cm)	16	(26.7%)	12	(19.4%)	6	(14.3%)	
Estimated blood loss Mean (SD)	529.5	(405.3)	619.7	(506.5)	738.9	(657.0)	0.271
Post-operative outcomes							
Transfusion need							0.320
Yes	16	(19.0%)	21	(25.0%)	9	(15.0%)	
No	68	(81.0%)	63	(75.0%)	51	(85.0%)	
Hospital stay Mean (SD)	7.3	(4.7)	7.9	(5.3)	8.7	(9.4)	0.371
Readmission							1.000
Yes	5	(6.0%)	5	(6.0%)	4	(6.7%)	
No	79	(94.0%)	74	(94.0%)	56	(93.3%)	
30-day mortality	5	(6.0%)	0	(0%)	2	(3.3%)	0.071
90-day mortality	7	(8.3%)	2	(2.4%)	2	(3.3%)	0.215

*: some patients experienced more than one complication; OR: operation room; SD: standard deviation; VTE: venous thromboembolism

found an inverse correlation between complexity and BMI, whereas Fotopoulou et al. found increased complexity in women with a higher BMI (8, 9). However, the majority did not show major significant differences in surgical radicality.

Body mass index and surgical morbidity

Data from five of the included studies was available for the meta-analysis comparing surgical morbidity of non-obese to obese ovarian cancer patients. Results are illustrated in Figure 1 and Figure S2. Obese ovarian cancer patients had an increased incidence of wound complications (P<0.001) with an odds rate (OR) of 4.81 (confidence interval (CI): 2.40 – 9.62). However, there were no significant differences in other individual complications including febrile morbidity, ileus, infection or sepsis, VTE (venous thromboembolism), pneumonia (Figure S2), return to operating room and organ failure, or total complications. Infection or sepsis, return to operation room and organ failure could only be assessed with data from our study and did not vary significantly (P=0.07, P=0.78, P=0.69), although infection or sepsis did show a trend towards a higher incidence among obese patients (P=0.07, OR: 2.05 CI: 0.95 – 4.43).

Body mass index and intra-operative outcomes

There were no differences between non-obese and obese patients in terms of operative outcomes including debulking status (complete cytoreduction (P=0.99, OR: 1.00 CI: 0.73 – 1.35), optimal cytoreduction (P=0.64, OR: 0.94 CI: 0.72 – 1.23) and operation time (P=0.67, OR: -6.11 CI: -34.49 – 22.27) (Figure S3). Estimated blood loss during surgery was greater in the obese group, but this did not reach significance (P=0.09) due to results of Suh et al. (Figure S3).

Body mass index and post-operative outcomes

Obese patients had a significant longer hospital stay (P=0.004) with a mean difference (MD) of 0.71 days (CI: 0.23 – 1.20). However, there was no difference in 30-day mortality (P=0.81, OR: 1.11 CI: 0.49 – 2.50) and transfusion rates (P=0.39, OR: 0.85 CI: 0.58 – 1.24) between the non-obese and obese group.

Furthermore, we compared BMI <25 kg/m^2 to morbidly obese patients (BMI ≥40 kg/m^2) in terms of surgical morbidity and outcomes using data available from Kumar et al. and our study (8). This revealed a significantly increased rate of organ failure (P=0.04 OR: 2.27 CI: 1.05 – 4.91) in the morbidly obese group. No other differences were found in other surgical complications, and intra- and post-operative outcomes (data not shown).

An additional analysis comparing patients with a BMI <25 kg/m^2 to overweight and obese women (BMI ≥25 kg/m^2) did not reveal any other significant differences in terms of operative morbidity, intra- and post-operative outcomes (Figure S4).

Table 3 Characteristics of included studies

Study	Study design	Number	Patients	BMI groups
Kumar et al. (8)	Retrospective study	620	Stage IIIc-IV	BMI <25 BMI 25-39.9 BMI ≥40
Matthews et al. (16)	Retrospective study	304	Stage II-IV	BMI <30 BMI ≥30 BMI <18.5 BMI 18.5-24.9 BMI 25-29.9 BMI 30-34.9 BMI ≥35
Suh et al. (17)	Retrospective study	486	Stage I-IV	Asian categories BMI <18.5 BMI 18.5-22.9 BMI 23-27.4 BMI ≥27.5 BMI <23.0 BMI ≥23.0
Fotopoulou et al. (9)	Prospective database study	306	Stage I-IV	BMI <25 BMI ≥25 BMI ≥30
Wolfberg et al. (18)	Retrospective case-control study	128	Stage III-IV	BMI <30 BMI ≥30
Our data	Retrospective study	228	Stage I-IV	BMI <25 BMI 25-29.9 BMI ≥30 BMI 30-39.9 BMI ≥40

EBL: estimated blood loss; ICU: intensive care unit; OR: operating room; OS: overall survival; PCS: packed cells; PFS: progression free survival

Risk of bias and confounding

Included studies were non-randomised with a retrospective design in the majority of studies, which leads to a high risk of bias associated with non-randomisation, selective reporting and patient attrition. Two studies, Kumar et al. and Fotopoulou et al., reported on possible confounding factors and adjusted for this in their analysis (8, 9), while the remaining studies only used univariate analyses. The majority of

Outcomes measures	Conclusion
Surgical complications 30-day mortality, 90-day mortality, OS, PFS EBL, OR time, debulking status Additional data: hospital stay, transfusion	BMI ≥ 40: ↑ grade 3 & 4 complications 90-day mortality worse in BMI <25 and ≥40 No difference in OS or PFS No difference in EBL, OR time, residual disease
Surgical complications OS, PFS, recurrence EBL, OR time, hospital stay, debulking status, transfusion	BMI ≥35: ↑ EBL BMI ≥30: ↑ wound complications No difference in other surgical complications No difference in OS or PFS. BMI ≥30: ↓ recurrence No difference in cytoreduction
Surgical complications OS, PFS, recurrence EBL, OR time, hospital stay, debulking status, transfusion (≥ 3 PCS)	BMI≥23: ↑ wound complications No difference in OS or PFS No difference in EBL, OR time, residual disease, hospital stay
Surgical complications 30-day mortality OS, PFS, recurrence, debulking status	No difference in complications or 30-day mortality No difference in OS or PFS BMI ≥25: ↑ OR time No difference in residual disease
Surgical complications EBL, OR time, hospital stay, ICU admission, debulking status, transfusion	No difference in complications BMI ≥30: ↑ ICU admission, ↓ OR time No difference in hospital stay or residual disease
Surgical complications 30-day mortality, 90-day mortality OS, recurrence EBL, hospital stay, debulking status, transfusion	No difference in complications, mortality, OS, recurrence, hospital stay, residual disease or transfusion

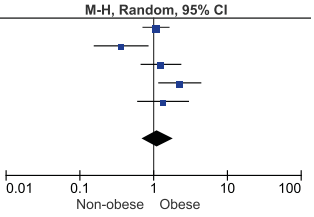
studies assessed surgical extent and complexity as a confounder and found no major differences between groups. In addition, the studies varied in disease stage inclusion, varying from all stage disease (I-IV) to only stage IIIc-IV, leading to heterogeneity of studies. We did not assess the quality of evidence using GRADE, as included studies were mainly retrospective studies.

Figure 1 Meta-analysis of surgical morbidity in non-obese versus obese patients

Total complications

Study or Subgroup	Obese Events	Obese Total	Non-Obese Events	Non-Obese Total	Weight	Odds Ratio M-H, Random, 95% CI
Kumar 2014	160	204	321	416	25.7%	1.08 [0.72, 1.61]
Matthews 2009	7	71	54	233	16.3%	0.36 [0.16, 0.84]
Our data	22	60	53	168	20.8%	1.26 [0.68, 2.33]
Suh 2012	15	52	66	434	20.0%	2.26 [1.17, 4.35]
Wolfberg 2004	25	38	53	90	17.2%	1.34 [0.61, 2.96]
Total (95% CI)		**425**		**1341**	**100.0%**	**1.12 [0.69, 1.83]**
Total events	229		547			

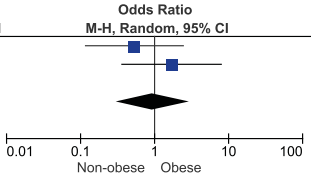
Heterogeneity: Tau² = 0.20; Chi² = 11.87, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 0.46 (P = 0.65)



Febrile complications

Study or Subgroup	Obese Events	Obese Total	Non-Obese Events	Non-Obese Total	Weight	Odds Ratio M-H, Random, 95% CI
Matthews 2009	2	71	12	233	50.7%	0.53 [0.12, 2.44]
Suh 2012	2	52	10	434	49.3%	1.70 [0.36, 7.96]
Total (95% CI)		**123**		**667**	**100.0%**	**0.94 [0.30, 2.98]**
Total events	4		22			

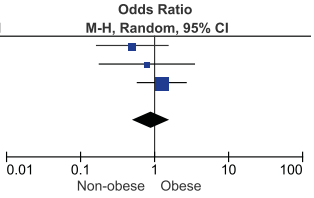
Heterogeneity: Tau² = 0.08; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 0.10 (P = 0.92)



Ileus

Study or Subgroup	Obese Events	Obese Total	Non-Obese Events	Non-Obese Total	Weight	Odds Ratio M-H, Random, 95% CI
Our data	4	60	21	168	27.0%	0.50 [0.16, 1.52]
Suh 2012	2	52	21	434	15.2%	0.79 [0.18, 3.46]
Wolfberg 2004	19	38	40	90	57.8%	1.25 [0.58, 2.67]
Total (95% CI)		**150**		**692**	**100.0%**	**0.91 [0.51, 1.62]**
Total events	25		82			

Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)



Wound complications

Study or Subgroup	Obese Events	Obese Total	Non-Obese Events	Non-Obese Total	Weight	Odds Ratio M-H, Random, 95% CI
Matthews 2009	8	71	4	233	31.6%	7.27 [2.12, 24.93]
Our data	2	60	0	168	5.2%	14.40 [0.68, 304.37]
Suh 2012	8	52	21	434	63.2%	3.58 [1.50, 8.55]
Total (95% CI)		**183**		**835**	**100.0%**	**4.81 [2.40, 9.62]**
Total events	18		25			

Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 4.44 (P < 0.00001)

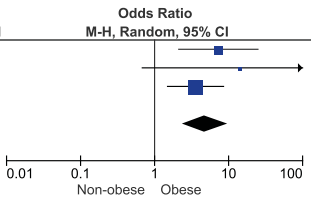
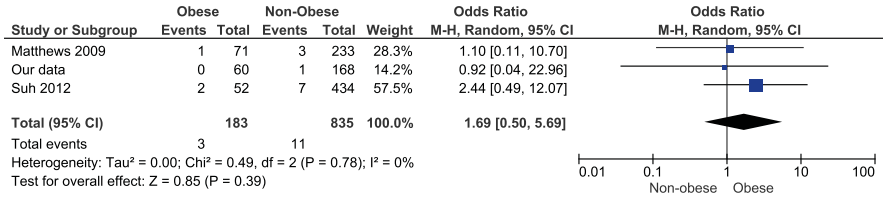


Figure 1 Continued

Venous thromboembolism



Discussion

Obesity affects more than one third of all ovarian cancer patients. It is important to assess its impact on ovarian cancer management and outcomes in order to improve current care, optimise recovery and minimize complications.

In current practice, it is a common belief that obese ovarian cancer patients are at increased surgical risk and a challenge for surgical feasibility, but a uniform guidance for their care is lacking. Studies have been conflicting in their reports on the effect of obesity on surgical outcomes in ovarian cancer, and outcomes have not been similar or comparable across studies (8, 9, 16-18). In addition, their small sample sizes limit the power of their conclusions.

Main findings

The main outcome of our institutional study is that BMI is associated with wound complications which occurred significantly more among the morbidly obese, but not other surgical outcomes. In addition, we systematically reviewed the literature on the impact of body mass index on surgical morbidity and outcomes in ovarian cancer patients. The review showed that an increasing BMI is associated with increased rates of wound complications and prolonged hospital stay, but did not influence other surgical complications. Surgical outcomes including complete and optimal debulking status, and 30-day mortality did not correlate with BMI status in the review. These outcomes generally concur with the findings of our institutional study. We did find a trend towards a prolonged hospital stay among obese patients in our study, but this did not reach significance, which may be due to the relatively small study population. In addition, short-term mortality did not differ significantly among the BMI groups, but women with BMI <25 kg/m^2 did have relatively higher mortality rates, which may be a result of the study population size.

The increased rate of wound complications and a prolonged hospital stay among obese patients has been well established by the literature (19, 20). Even though these are not considered major complications, they may negatively influence recovery and delay adjuvant therapy and are therefore important to take into account.

In other gynaecological cancers, the majority of studies suggest that mild to moderate obesity (BMI 30-39.9 kg/m^2) does not result in increased surgical complications other than wound complications (20-22). The majority of surgical outcomes also appear to be similar to normal weight patients, with varying reports on estimated blood loss and operating time (21, 23). Furthermore, the feasibility of obtaining complete or optimal cytoreduction and 30-day mortality does not seem to vary among different BMI groups (22). Ninety-day mortality is not often used as an indicator of mortality post-treatment, even though it is an important outcome especially in ovarian cancer where the average 1-year survival is only 72% (24). Therefore its use in future studies should be encouraged.

Morbidly obese women with ovarian cancer have recently been suggested to be at increased risk of severe complications and mortality (8). We found a trend towards poorer outcomes in this group, but we cannot provide a definite conclusion due to small number of morbidly obese in our study. Unfortunately, most studies in the literature have not specifically looked at the influence of morbid obesity (BMI ≥40 kg/m^2). However, Kumar et al. presented the results of a large homogenous group of advanced stage (IIIc-IV) ovarian cancer patients, showing a significantly higher risk of operative complications and mortality among the morbidly obese (8). This strongly suggests that women at the extremes of weight, i.e. BMI ≥40 kg/m^2, are at increased risk of surgical morbidity and poorer surgical outcomes. In addition, studies in endometrial cancer support that especially the morbidly obese patients are at increased risk of surgical complications including wound complications, infectious complications, venous thrombophlebitis and prolonged hospital stay (20-22, 25). Future research should focus specifically on this group within the ovarian cancer population, to develop appropriate guidelines for future care.

Strengths and limitations

Completeness and applicability of evidence

The search identified five studies and we included our own study in the review. The majority of women were diagnosed with stage II-IV disease, which is consistent with reported incidence rates (26). The BMI groups assessed varied significantly among studies, and corresponding authors of three studies were contacted for additional data. We received the raw data from one (8), leading to an inclusion of five of the six studies in the meta-analysis comparing non-obese versus obese patients, five studies comparing BMI <25 kg/m^2 to BMI ≥25 kg/m^2, and two studies comparing BMI <25 kg/m^2 to morbidly obese. The studies evaluated a variety of surgical

complications of which the majority could be equated in the meta-analysis. However, several intra- and post-operative outcomes were assessed by few studies, and therefore no definite conclusions could be drawn.

Quality of evidence

The included studies were at a high risk of bias, mainly because of their retrospective design and the fact that the majority did not adjust for possible confounding factors. In addition, there was a lack of uniformity in reporting surgical morbidity and outcomes. There was considerable heterogeneity among the populations studied, especially in terms of stage of disease. As stage of disease and corresponding surgical management are well known to correlate with risk of operative morbidity and mortality, it is possible that a negative effect of obesity on surgical outcomes is weakened by the inclusion of studies evaluating all stage disease. Well-designed prospective studies are therefore recommended to assess the impact of obesity on operative outcomes, especially in the less prevalent morbidly obese ovarian cancer patients, and within high-risk populations such as patients with disseminated disease.

Potential biases in review process

A comprehensive search of the literature was performed by the two reviewers, and included a search of the grey literature. Potentially eligible papers were independently reviewed by the two reviewers. Differences were resolved by appeal to a third reviewer (AL).

Interpretation

BMI and pre-existing comorbidities are factors used in the pre-assessment for ovarian cancer. However, we found no compelling evidence for modifying or limiting the extent of surgical radicality based on BMI to reduce operative morbidity and adverse outcomes; although there may be some technical limitations to performing surgery in some patients. Impaired wound healing is a well-recognised and important issue among obese patients, and should be taken into account when planning post-operative care.

Conclusion

We found that an increasing BMI is associated with wound complications in ovarian cancer surgery. However, BMI does not appear to affect other operative outcomes including cytoreduction status and 30-day mortality. We therefore conclude that operative management and post-operative care should not be based on body mass index alone, but requires a multifactorial approach to minimise adverse outcomes.

In addition, the significance of morbid obesity still remains unclear and should be assessed in well-designed future studies to determine if this specific group of patients is at risk of increased operative morbidity and adverse outcomes.

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Appendix S1 – Search strategy

1. OVARIAN NEOPLASMS
2. “ovar* cancer*”
3. “ovar* neoplasm*”
4. “ovar* tumour*”
5. “ovar* tumor*”
6. 1 OR 2 OR 3 OR 4 OR 5
7. OBESITY
8. obes*
9. weight
10. “body mass index”
11. “BMI”
12. BODY MASS INDEX
13. “quetelet index”
14. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. GYNECOLOGY
16. surger*
17. operati*
18. cytoreduct*
19. debulk*
20. 15 OR 16 OR 17 OR 18 OR 19
21. POSTOPERATIVE COMPLICATIONS
22. “post operative complication*”
23. “operative complication*”
24. “complication*”
25. “operative morbid*”
26. “surg* complication*”
27. “surg* morbid*”
28. DEATH
29. death
30. mortality
31. morbidity
32. SURVIVAL
33. survival
34. “operative outcom*”
35. “surgical outcom*”
36. 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35
37. 6 AND 14 AND 20 AND 36

Figure S1 PRISMA Flow diagram for selection of studies

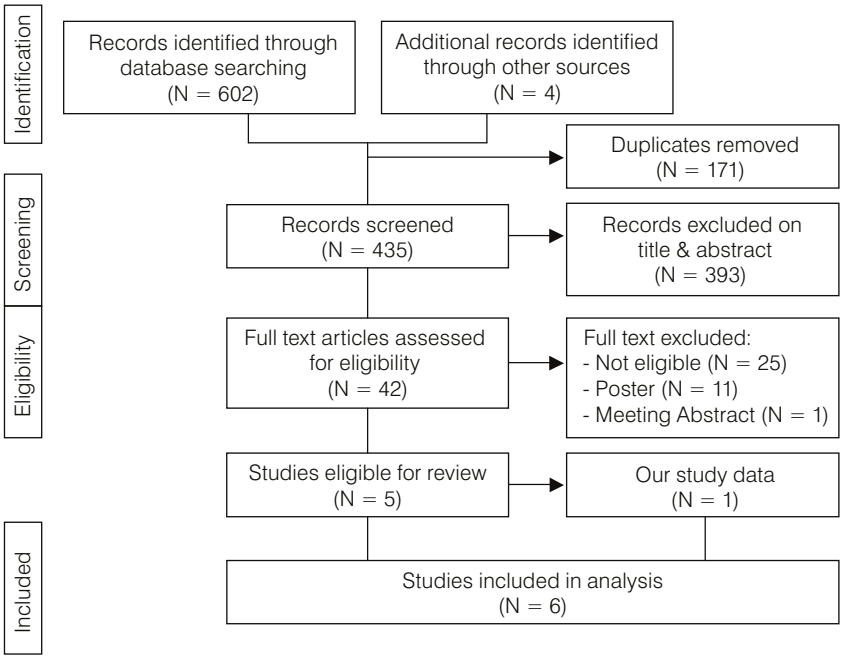


Figure S2 Meta-analysis of surgical morbidity in non-obese versus obese patients - supplement

Pneumonia

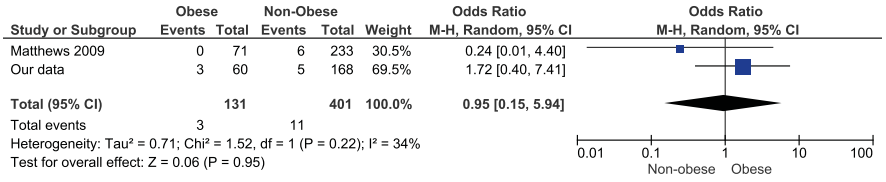
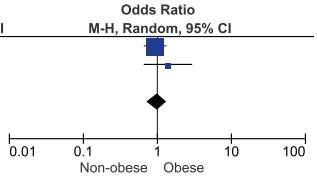


Figure S3 Meta-analysis of intra-operative outcomes of non-obese versus obese patients

Complete cytoreduction

Study or Subgroup	Obese Events	Obese Total	Non-obese Events	Non-obese Total	Weight	Odds Ratio M-H, Random, 95% CI
Kumar 2014	91	204	193	416	82.7%	0.93 [0.66, 1.30]
Our data	28	42	72	122	17.3%	1.39 [0.67, 2.90]
Total (95% CI)		**246**		**538**	**100.0%**	**1.00 [0.73, 1.35]**
Total events	119		265			

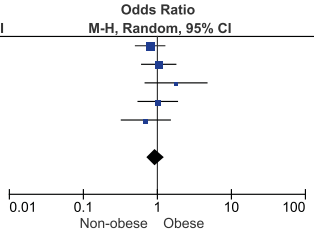
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)



Optimal cytoreduction

Study or Subgroup	Obese Events	Obese Total	Non-obese Events	Non-obese Total	Weight	Odds Ratio M-H, Random, 95% CI
Kumar 2014	169	204	357	416	34.8%	0.80 [0.51, 1.26]
Matthews 2009	37	71	119	233	25.6%	1.04 [0.61, 1.77]
Our data	36	42	94	122	7.8%	1.79 [0.68, 4.68]
Suh 2012	35	52	291	434	19.3%	1.01 [0.55, 1.87]
Wolfberg 2004	19	38	53	90	12.5%	0.70 [0.33, 1.50]
Total (95% CI)		**407**		**1295**	**100.0%**	**0.94 [0.72, 1.23]**
Total events	296		914			

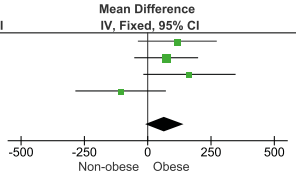
Heterogeneity: Tau² = 0.00; Chi² = 3.00, df = 4 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)



Estimated blood loss

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Non-obese Mean	Non-obese SD	Non-obese Total	Weight	Mean Difference IV, Fixed, 95% CI
Kumar 2014	1,184	969	204	1,067	803	416	24.9%	117.00 [-36.74, 270.74]
Matthews 2009	556	476	71	483	435	233	38.2%	73.00 [-51.01, 197.01]
Our data	738.9	657	60	574	458.8	168	18.1%	164.90 [-15.24, 345.04]
Suh 2012	957	579.8	52	1,063.9	848.6	434	18.8%	-106.90 [-283.56, 69.76]
Total (95% CI)			**387**			**1251**	**100.0%**	**66.71 [-9.94, 143.36]**

Heterogeneity: Chi² = 5.27, df = 3 (P = 0.15); I² = 43%
Test for overall effect: Z = 1.71 (P = 0.09)



Operation time

Study or Subgroup	Obese Mean	Obese SD	Obese Total	Non-obese Mean	Non-obese SD	Non-obese Total	Weight	Mean Difference IV, Random, 95% CI
Kumar 2014	274	101	204	271	107	416	33.6%	3.00 [-14.26, 20.26]
Matthews 2009	113.3	47.9	71	99.1	47.8	233	35.6%	14.20 [1.48, 26.92]
Suh 2012	228	78	52	267.6	90	434	30.7%	-39.60 [-62.43, -16.77]
Total (95% CI)			**327**			**1083**	**100.0%**	**-6.11 [-34.49, 22.27]**

Heterogeneity: Tau² = 546.12; Chi² = 16.30, df = 2 (P = 0.0003); I² = 88%
Test for overall effect: Z = 0.42 (P = 0.67)

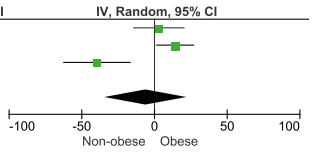
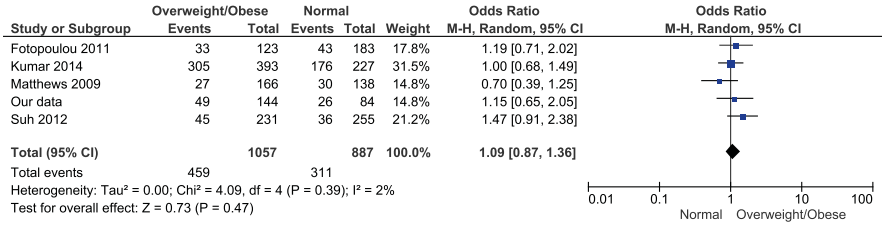


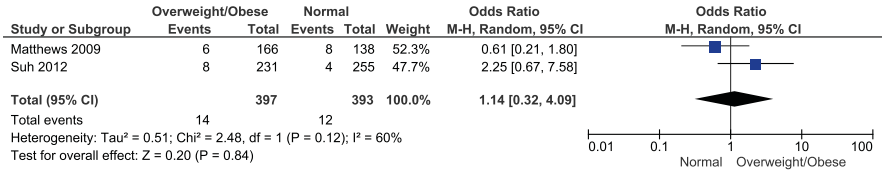
Figure S4 Meta-analysis of surgical morbidity and outcomes when comparing BMI < 25 kg/m² to BMI ≥ 25 kg/m²

Surgical morbidity

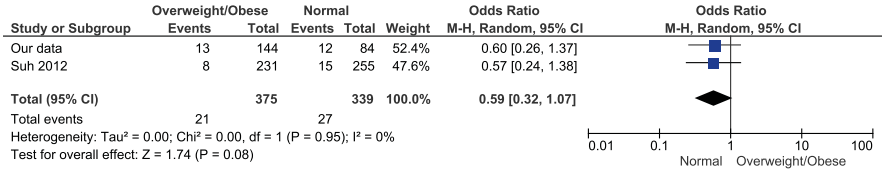
Total complications



Febrile complications



Ileus



Wound complications

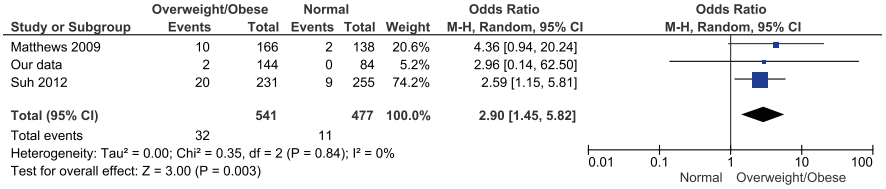
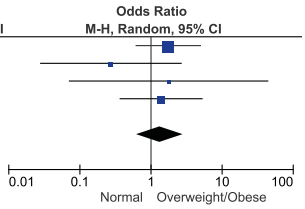


Figure S4 Continued

Venous thromboembolism

Study or Subgroup	Overweight/Obese Events	Total	Normal Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Fotopoulou 2011	8	123	7	183	51.8%	1.75 [0.62, 4.95]
Matthews 2009	1	166	3	138	10.9%	0.27 [0.03, 2.65]
Our data	1	144	0	84	5.4%	1.77 [0.07, 43.86]
Suh 2012	5	231	4	255	31.9%	1.39 [0.37, 5.23]
Total (95% CI)		**664**		**660**	**100.0%**	**1.33 [0.63, 2.81]**
Total events	15		14			

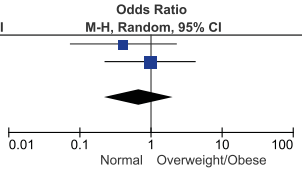
Heterogeneity: Tau² = 0.00; Chi² = 2.18, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)



Pneumonia

Study or Subgroup	Overweight/Obese Events	Total	Normal Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Matthews 2009	2	166	4	138	42.0%	0.41 [0.07, 2.26]
Our data	5	144	3	84	58.0%	0.97 [0.23, 4.17]
Total (95% CI)		**310**		**222**	**100.0%**	**0.68 [0.22, 2.05]**
Total events	7		7			

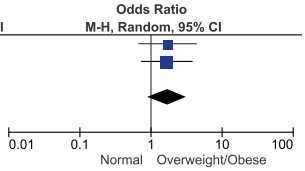
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.69 (P = 0.49)



Infection or sepsis

Study or Subgroup	Overweight/Obese Events	Total	Normal Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Fotopoulou 2011	10	123	9	183	43.6%	1.71 [0.67, 4.34]
Our data	24	144	9	84	56.4%	1.67 [0.74, 3.78]
Total (95% CI)		**267**		**267**	**100.0%**	**1.69 [0.91, 3.12]**
Total events	34		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)



Return to operating room

Study or Subgroup	Overweight/Obese Events	Total	Normal Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Fotopoulou 2011	10	123	9	183	34.0%	1.71 [0.67, 4.34]
Kumar 2014	27	393	22	227	59.3%	0.69 [0.38, 1.24]
Our data	2	144	1	84	6.7%	1.17 [0.10, 13.09]
Total (95% CI)		**660**		**494**	**100.0%**	**0.97 [0.51, 1.85]**
Total events	39		32			

Heterogeneity: Tau² = 0.09; Chi² = 2.68, df = 2 (P = 0.26); I² = 25%
Test for overall effect: Z = 0.09 (P = 0.93)

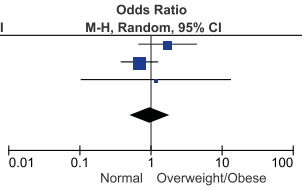
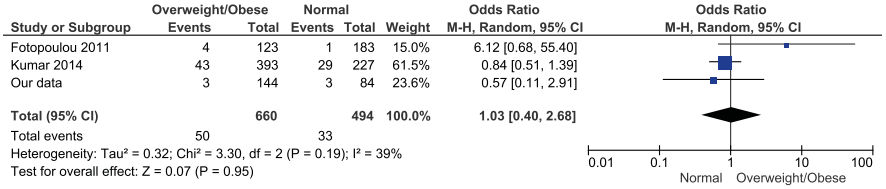


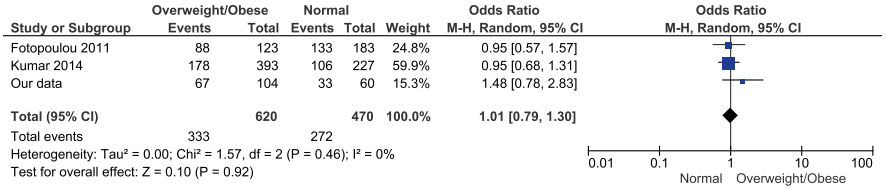
Figure S4 Continued

Organ failure

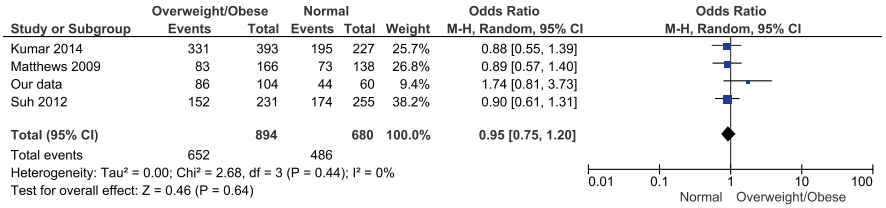


Intra- and post-operative outcomes

Complete cytoreduction



Optimal cytoreduction



Estimated blood loss

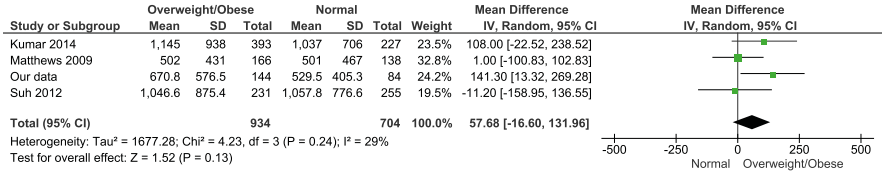
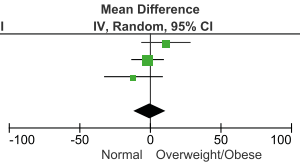


Figure S4 Continued

Operation time

Study or Subgroup	Overweight/Obese Mean	SD	Total	Normal Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kumar 2014	276	106	393	265	104	227	29.1%	11.00 [-6.11, 28.11]
Matthews 2009	101	45	166	103	53	138	48.4%	-2.00 [-13.18, 9.18]
Suh 2012	258	108	231	270	122	255	22.5%	-12.00 [-32.45, 8.45]
Total (95% CI)			**790**			**620**	**100.0%**	**-0.46 [-11.54, 10.63]**

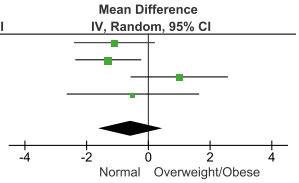
Heterogeneity: Tau² = 33.52; Chi² = 3.02, df = 2 (P = 0.22); I² = 34%
Test for overall effect: Z = 0.08 (P = 0.94)



Hospital stay

Study or Subgroup	Overweight/Obese Mean	SD	Total	Normal Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kumar 2014	9	7.2	393	10.1	8.3	227	27.9%	-1.10 [-2.39, 0.19]
Matthews 2009	4.8	2.1	166	6.1	6	138	32.8%	-1.30 [-2.35, -0.25]
Our data	8.3	7.3	144	7.3	4.7	84	23.3%	1.00 [-0.56, 2.56]
Suh 2012	19.2	10	231	19.7	13.8	255	16.0%	-0.50 [-2.63, 1.63]
Total (95% CI)			**934**			**704**	**100.0%**	**-0.58 [-1.62, 0.46]**

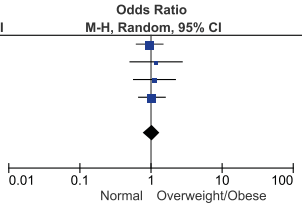
Heterogeneity: Tau² = 0.56; Chi² = 6.22, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 1.10 (P = 0.27)



Transfusion

Study or Subgroup	Overweight/Obese Events	Total	Normal Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Kumar 2014	323	393	188	227	37.5%	0.96 [0.62, 1.47]
Matthews 2009	14	166	10	138	9.8%	1.18 [0.51, 2.74]
Our data	30	144	16	84	15.2%	1.12 [0.57, 2.20]
Suh 2012	51	231	55	255	37.5%	1.03 [0.67, 1.59]
Total (95% CI)		**934**		**704**	**100.0%**	**1.03 [0.79, 1.34]**
Total events	418		269			

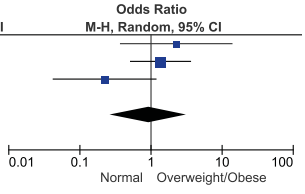
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.84)



30-day mortality

Study or Subgroup	Overweight/Obese Events	Total	Normal Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Fotopoulou 2011	3	123	2	183	26.5%	2.26 [0.37, 13.74]
Kumar 2014	14	393	6	227	44.6%	1.36 [0.52, 3.59]
Our data	2	144	5	84	29.0%	0.22 [0.04, 1.17]
Total (95% CI)		**660**		**494**	**100.0%**	**0.92 [0.27, 3.15]**
Total events	19		13			

Heterogeneity: Tau² = 0.64; Chi² = 4.32, df = 2 (P = 0.12); I² = 54%
Test for overall effect: Z = 0.13 (P = 0.90)



7

QUALITY OF LIFE OF OVARIAN CANCER SURVIVORS: THE INFLUENCE OF OBESITY

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Abstract

Objective

Recent advances in the treatment of gynaecological cancer have led to improved survival rates putting a greater emphasis on issues such as the quality of life. In this study, we evaluated the effect of body mass index (BMI) on the quality of life of ovarian cancer survivors.

Methods

Women diagnosed with ovarian cancer at the Royal Cornwall Hospital Trust between January 2008 and May 2013 were identified. Ovarian cancer survivors were invited to participate by completing the EORTC QLQ-C30 (quality of life) questionnaire. Univariate and multiple regression analyses were used to determine associations between BMI and quality of life outcomes.

Results

176 ovarian cancer survivors were invited to participate of which 133 were eligible for this study. In total, 81 ovarian cancer survivors (60.4%) completed the questionnaire, of which 26 responders (32.1%) were overweight (BMI 25-29.9 kg/m^2) and 27 (33.3%) were obese (BMI ≥30 kg/m^2). Increasing BMI was significantly associated with poorer quality of life outcomes in terms of physical functioning and emotional functioning, and this effect persisted for physical functioning after multiple regression analysis.

Conclusion

Increasing BMI is associated with poorer quality of life outcomes in terms of physical and emotional functioning in ovarian cancer survivors. Further research is needed to evaluate the association between BMI and quality of life from diagnosis to survivorship in order to develop novel interventions.

Background

Ovarian cancer is the seventh most common cancer in women worldwide with an estimated 239,000 new cases diagnosed in 2012. Despite having one of the lowest survival rates amongst the common cancers, in the UK the five-year relative survival for ovarian cancer has doubled in the last 30 years from 22% in 1976-80 to 43% in 2005-09 (1), similar to 5 year survival in the USA (44.6%) (2). With improving survival rates, there is now a greater emphasis on efforts to maximise the quality of life and psychological health of ovarian cancer survivors.

Although a high body mass index (BMI) has been shown to negatively impact quality of life outcomes in gynaecological cancer survivors (3, 4), there have been no studies evaluating the association between BMI and quality of life in ovarian cancer survivors. Recent years have witnessed a dramatic increase in obesity in women in England with 57% of women being overweight or obese in 2012, and these number are still expected to rise (5). Obesity has been shown to negatively affect ovarian cancer patients during other aspects of the trajectory of the disease including treatment outcomes and survival (6-9).

In this study, we aimed to assess the effect of body mass index on the quality of life of ovarian cancer survivors.

Methods

Study population

Women diagnosed with ovarian cancer at the Royal Cornwall Hospital Trust (RCHT) between January 2008 and May 2013 were identified from the Cancer Registry of the South West Cancer Intelligence Service. Women who had completed primary treatment were approached to participate in a departmental review of follow-up care. This evaluated the quality of care and holistic needs assessment of the gynaecological oncology service at the RCHT. Women were sent an introduction letter accompanied by a patient satisfaction questionnaire as well as a quality of life questionnaire. Consent was given by completing and returning the questionnaires to the RCHT with a pre-paid envelope. We performed a secondary analysis of factors associated with quality of life outcomes in follow-up care. Included in this analysis were women who had a known BMI at time of diagnosis. We excluded women with borderline ovarian tumors, a history of concurrent cancer, or if they had received treatment elsewhere.

Data collection

Baseline and clinical characteristics such as age, performance status at diagnosis (ECOG) (10), disease stage (FIGO) (11), grade, treatment, recurrent disease, time from diagnosis and other characteristics had been collected retrospectively from the patients' medical records. Body mass index (weight (kg) / [height (m)]^2) at time of diagnosis was categorized according to national guidelines, respectively; underweight (≤18.5 kg/m^2), normal (18.5-24.9 kg/m^2), obese category I (30-34.9 kg/m^2), obese category II (35-39.9 kg/m^2) and category III (morbidly obese; ≥40 kg/m^2) (12). The project was a secondary analysis within a departmental service evaluation of the follow up care of the RCHT, and therefore did not require formal ethical review.

Measures

Quality of life was assessed with the 30-item questionnaire (QLQ-C30, version 3.0) of the European Organization for Research and Treatment of Cancer (EORTC). This is a validated, self-reporting, cancer-specific questionnaire composed of both multi-item scales and single-item measures. It covers several areas of quality of life; physical, role, emotional, cognitive, and social functioning as well as symptom distress and global quality of life (13). Higher scores for functional scales and global quality of life represent a higher level of functioning and a high quality of life. Higher scores for symptom scales or items represent a higher level of symptomatology (14).

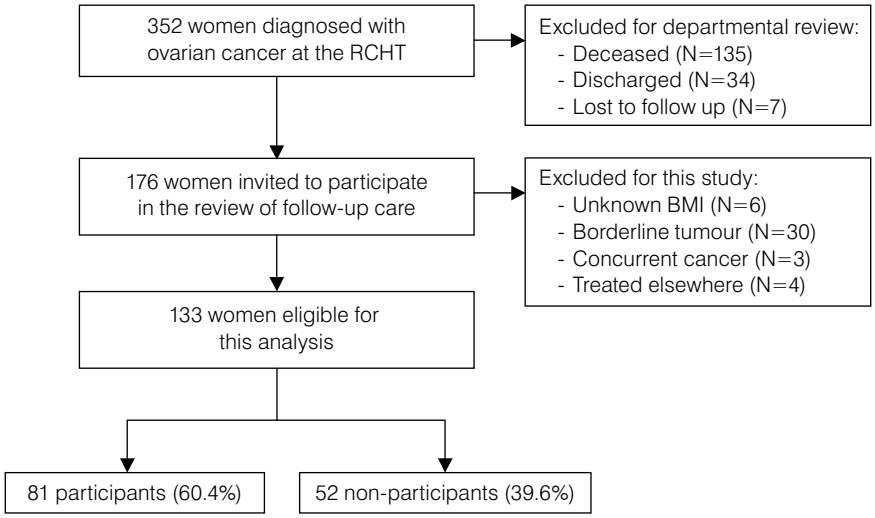
Statistical analysis

Data were analysed with SPSS statistics version 20.0 (15). Body mass index was categorized in three categories for analysis purposes, respectively; normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2). Continuous outcomes were presented as means with standard deviations (SD), categorical outcomes were presented as frequencies and proportions. Baseline and clinical characteristics were compared using nonparametric tests for continuous data, and Pearson's Chi-Square and Fisher's exact test for categorical variables. The EORTC QLQ-C30 outcomes were analyzed according to scoring procedures and were linearly transformed into 0-100 scales (14). Univariate and multiple regression analyses were used to assess primary associations between body mass index and quality of life outcomes, while taking into consideration other baseline and clinical characteristics of influence. P-values were regarded significant if $p<0.05$ and tests were two-sided.

Results

A total of 352 women were diagnosed with ovarian cancer in the RCHT between January 2008 and May 2013, of which 135 were deceased, 34 were discharged from follow up, and seven were lost to follow up. Consequently, 176 women diagnosed with ovarian cancer were invited to participate in the departmental review. Excluded from further analysis in this study were six women with unknown BMI, 30 women with borderline tumors (on review of histology), three with concurrent cancer, and four women who were treated elsewhere. Of the remaining 133 ovarian cancer survivors, 81 (60.4%) had completed the questionnaire (the participants) and 52 women had failed to return them (the non-participants) (Figure 1).

Figure 1 Flow chart of recruitment



Baseline and clinical characteristics

The mean age of women participating in the study was 63 years (SD 11.2). The majority (67.9%) of women were diagnosed with late stage (III and IV) ovarian cancer. Almost all women had undergone surgery (91.4%) and/or chemotherapy (86.5%). The median time from diagnosis to study participation was 20 months (range 0 – 172). The overall recurrence rate was 21%, with 12.5% recurrence in women with early stage disease and 25.5% in late stage disease (data not shown). The median time to

recurrence was 27 months (range 8 - 87). Participants did not differ in baseline and clinical characteristics compared to non-participants (data not shown).

Baseline and clinical characteristics of women who returned the questionnaires are presented in Table 1 according the BMI categories. Twenty-eight women (34.6%) had a normal BMI, 26 women (32.1%) were overweight and a further 27 women (33.3%) were obese. Of the 27 obese women, 17 women were in obese category I (BMI 30-34.9 kg/m^2), seven women in obese category II (BMI 35-39.9 kg/m^2) and three women were morbidly obese (category III; BMI ≥40 kg/m^2). Overweight women were significantly older than women with a normal BMI (P=0.032). Women did not significantly differ in other baseline and clinical characteristics among the different BMI categories, including the type and complexity of surgical treatment (e.g. lymphadenectomy (P=0.083) and bowel resection (P=0.650)).

Body mass index and quality of life outcomes

Quality of life outcomes of ovarian cancer survivors are presented as mean scores (SD) according to the BMI categories (Table 2). Women with a normal BMI reported the highest global quality of life scores, but this did not differ significantly among different BMI categories (P=0.525). Women with increased BMI had significantly poorer physical functioning (P=0.042), which remained significant in the multiple regression analysis (P=0.005) after controlling for significant baseline and clinical characteristics including age, disease stage, treatment and recurrence. In addition, a higher BMI was associated with significantly poorer emotional functioning (P=0.022), but this did not persist in the regression analysis (P=0.051). Appetite loss was significantly higher among overweight ovarian cancer survivors (P=0.036). However, role, cognitive and social functioning did not vary significantly among the different BMI categories, and other symptom distress scores did show a significant association with BMI.

Table 1 Baseline and clinical characteristics participants according to BMI categories

	Normal (18.5-24.9 kg/m²) N=28		Overweight (25-29.9 kg/m²) N=26		Obese (≥30 kg/m²) N=27		Analysis P-value
Age (mean, range)	59	(31 - 84)	67	(44 - 84)	64	(37 - 79)	0.032*
Performance status (ECOG)							0.197
0	18	(64.3%)	18	(69.2%)	14	(51.9%)	
1	5	(17.9%)	3	(11.5%)	7	(25.9%)	
2-4	0	(0%)	1	(3.8%)	4	(14.8%)	
Unknown	5	(17.9%)	4	(15.4%)	2	(7.4%)	
Stage							0.140
Early (I-II)	10	(35.7%)	3	(11.5%)	11	(40.7%)	
Late (III-IV)	17	(60.7%)	22	(84.6%)	16	(59.3%)	
Unknown	1	(3.6%)	1	(3.8%)	0	(0%)	
Grade							0.100
Low (I)	2	(7.1%)	2	(7.7%)	3	(11.1%)	
High (2/3)	25	(89.3%)	18	(69.2%)	23	(85.2%)	
Unknown	1	(3.6%)	6	(23.1%)	1	(3.7%)	
Surgery							0.300
Yes	26	(92.9%)	22	(84.6%)	26	(96.3%)	
No	2	(7.1%)	4	(15.4%)	1	(3.7%)	
Residual disease							0.676
None	18	(64.4%)	13	(50.0%)	20	(74.1%)	
< 1 cm	3	(10.7%)	4	(15.4%)	2	(7.4%)	
≥ 1 cm	4	(14.3%)	5	(19.2%)	3	(11.1%)	
Unknown	1	(3.6%)	0	(0%)	1	(3.7%)	
Not applicable	2	(7.1%)	4	(15.4%)	1	(3.7%)	
Chemotherapy							0.995
Yes	25	(89.3%)	23	(88.5%)	24	(88.9%)	
No	3	(10.7%)	3	(11.5%)	3	(11.1%)	
Time from diagnosis							0.635
< 1 year	10	(35.7%)	8	(30.8%)	7	(25.9%)	
1 - < 2 years	8	(28.6%)	8	(30.8%)	5	(18.5%)	
2 - < 3 years	2	(7.1%)	3	(11.5%)	5	(18.5%)	
3 - < 4 years	2	(7.1%)	1	(3.8%)	4	(14.8%)	
≥ 4 years	6	(21.4%)	6	(23.1%)	6	(22.2%)	
Recurrence							0.364
Yes	4	(14.3%)	5	(19.2%)	8	(29.6%)	
No	24	(85.7%)	21	(80.8%)	19	(70.4%)	

*: P-value <0.05

Table 2 Quality of life outcomes according to BMI categories

	Normal (18.5-24.9 kg/m²) N=28	Overweight (25-29.9 kg/m²) N=26	Obese (≥30 kg/m²) N=27	Univariate analysis	Multiple regression
	Means (SD)			P-value	P-value
Global quality of life	67.9 (25.9)	62.0 (30.0)	58.6 (28.6)	0.525	
Functional scales					
Physical functioning	84.7 (18.2)	70.3 (25.7)	65.7 (30.6)	0.042*	0.005*
Role functioning	74.4 (29.9)	67.3 (29.2)	62.2 (34.5)	0.362	
Emotional functioning	80.7 (20.0)	86.3 (20.8)	69.8 (27.3)	0.022*	0.051
Cognitive functioning	82.7 (23.8)	81.3 (25.1)	78.8 (23.4)	0.755	
Social functioning	72.6 (31.5)	70.7 (34.1)	62.8 (37.8)	0.594	
Symptom scales					
Fatigue	31.3 (30.4)	40.4 (31.9)	41.2 (33.7)	0.460	
Nausea and vomiting	9.5 (23.3)	21.3 (35.5)	11.5 (14.7)	0.260	
Pain	22.2 (31.0)	16.7 (25.0)	30.7 (34.9)	0.362	
Dyspnoea	15.5 (24.8)	26.9 (28.3)	22.2 (29.2)	0.245	
Insomnia	25.9 (25.0)	26.9 (31.3)	29.6 (32.5)	0.951	
Appetite loss	14.3 (32.0)	33.3 (36.5)	18.5 (26.7)	0.036*	N/A
Constipation	25.0 (32.2)	21.8 (26.6)	16.0 (29.8)	0.328	
Diarrhoea	10.7 (24.1)	14.7 (23.7)	17.9 (34.3)	0.597	
Financial difficulties	11.9 (22.6)	8 (17.4)	17.3 (29.1)	0.439	

N/A: not applicable; SD: standard deviation; *: P-value <0.05

Discussion

Cancer diagnosis and treatment represent a tremendous impact on the physical and mental wellbeing of patients. Quality of life is therefore an important outcome for women surviving cancer. Over the past years, the impact of BMI on the quality of life of gynaecological cancer survivors has become an important focus of research. In women undergoing gynaecological oncology surgery, an increasing BMI has been associated with poorer quality of life outcomes (3).

In endometrial cancer, which is inextricably associated with obesity, the influence of BMI on the quality of life of survivors has been well established, with obese endometrial cancer survivors reporting a poorer quality of life in almost all functioning scales, especially physical functioning (4, 16-19). We recently reported that this global deterioration was most significant in the morbidly obese women in this patient population (4).

However, no studies have evaluated associations between body mass index and quality of life outcomes of ovarian cancer survivors to date. The purpose of this study was to assess the association between body mass index and quality of life of ovarian cancer survivors. As in previous studies, 34.6% of the participants in our study had a normal body mass index, 32.1% were overweight and a further 33.3% were obese at time of diagnosis (3, 20).

Interestingly, BMI did not influence global quality of life and several functioning scales in our patient group, unlike in endometrial cancer survivors, as mentioned above. This is probably explained by the small number of morbidly obese women (3.7%) in the current analysis of ovarian cancer survivors, compared to 19% in our endometrial cancer population (4).

Our study does show that overweight ovarian cancer survivors experience more appetite loss than their normal weight or obese counterparts. Although an interesting finding, we have not found validation for this in the literature and further investigation may be warranted.

We have found, as with endometrial cancer survivors, that an increasing BMI is significantly associated with poorer physical functioning. This effect persists even when taking other relevant patient characteristics into account such as stage, treatment and recurrent disease, which have been reported to influence the quality of life of ovarian cancer survivors (21-24). We can hypothesise that this area of quality of life is affected through limited mobility, restricted physical endurance and obesity-associated comorbidities (25-27).

General population studies have reported a reduced physical functioning among obese individuals across the obese BMI categories (I, II and III), with mean deteriorations of 2.54 (category I) up to 9.72 points (category III) when compared to normal weight (28). Therefore, obese women who develop ovarian cancer may have

a poorer quality of life than their normal weight counterparts. However, our study found a greater deterioration of physical functioning (MD; 19.0 points) among all obese women, with the majority being category I. This may reflect the additional burden of ovarian cancer on quality of life outcomes in our patients, which causes a greater quality of life deterioration among its overweight and obese survivors. Therefore, interventions aiming to increase physical activity may have an impact on quality of life in ovarian cancer survivors.

Trials in cancer survivors have shown that physical activity and a healthy diet improve overall cancer outcomes and are associated with improved quality of life throughout all BMI categories (29-34). Lifestyle intervention trials introducing exercise programs and improved diet in gynaecological cancer survivors are also showing promising results, but few have been undertaken in the ovarian cancer population even though the majority expressing an interest in participating in such programs (35-40).

Despite a less distinct effect of BMI on quality of life outcomes in ovarian cancer survivors, developing integrative approaches to support healthy lifestyles in ovarian cancer survivors is still important; taking into consideration that BMI has an impact on overall survival (8, 9). Our preliminary results suggest that novel survivorship interventions for maintaining a high quality of life should be directed at the survivor population as a whole, and that its focus should not lie on obese ovarian cancer survivors alone.

The strengths of our study include the use of a well-established and validated questionnaire to assess quality of life, and the use of measured weight and height to calculate body mass index. In addition, we presented data of both participants and non-participants which showed no significant differences, increasing the applicability of our study results.

A potential limitation of our study is the relatively small sample size, even though this is expected because of high mortality rates in ovarian cancer (1). The response rate (60.4%) was considered acceptable and in line with previous reported rates (4, 23). Furthermore, we did not have information regarding socio-demographic variables, sexual function and comorbidities, which may further influence the quality of life of ovarian cancer survivors (21, 41, 42). The validated EORTC ovarian cancer (OV28) module evaluates sexual functioning, but was not used in the departmental review (43).

Further evaluation of the relationship between body mass index and quality of life of ovarian cancer patients is needed, preferably through prospective studies evaluating quality of life throughout the trajectory of the disease.

Conclusion

We found that an increasing BMI is associated with poorer quality of life in terms of physical functioning of ovarian cancer survivors. Global quality of life and other functional scales did not show a significant association with BMI. Even though our preliminary study suggests a less defined relation between obesity and quality of life outcomes in ovarian cancer survivors, further evaluation of this relationship is needed. Development of novel interventions to enhance the quality of life of survivors may be an important next step in the care for ovarian cancer survivors, although its exact focus still remains unclear.

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8

BMI, PHYSICAL ACTIVITY AND QUALITY OF LIFE OUTCOMES IN OVARIAN CANCER SURVIVORS: TIME TO GET MOVING?

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Abstract

Objective

To evaluate the association between body mass index (BMI), physical activity (PA) and the quality of life (QoL) of ovarian cancer survivors.

Methods

We performed a two-centre cross-sectional study of women who had been treated for ovarian cancer between January 2007 and December 2014 at the Royal Cornwall Hospital Trust and the Plymouth Hospitals NHS Trust. QoL was assessed using the EORTC QLQ-C30 and QLQ-OV28 questionnaires, and PA using the Godin Leisure Time Exercise questionnaire.

Results

In total, 293 ovarian cancer survivors were invited to participate, of which 209 women (71.3%) responded. Thirty-five percent of women were overweight and 18% were obese, whilst only 21% met recommendations for PA. Obesity was associated with significantly poorer global QoL, physical, cognitive and social functioning, a poorer body image and more symptomatology. Sedentary behaviour was associated with poorer QoL scores including global QoL, physical, role, social and sexual functioning. After adjustment, BMI and PA both remained independently associated with QoL scores.

Conclusion

Obesity and inactivity are associated with poorer QoL among ovarian cancer survivors. Future interventions promoting PA and weight loss should be evaluated as possible means to improve the QoL of this population.

Background

Ovarian cancer is the fifth most common cancer in the UK, with a five-year survival of 43% (1). Over the past 30 years, the survival rate has almost doubled due to the improving treatment options (2, 3). Research has shown that cancer survivors experience poorer health related quality of life (QoL) compared to women in the general population, with treatment related-sequelae and the psychological aftermath of facing cancer diagnosis (4-6). In several cancer sites including breast and endometrial cancer, these poorer QoL outcomes have been linked to increased body mass index (BMI) and inactivity, laying the foundation for survivorship interventions (7-9).

In ovarian cancer, more than half of the patients are overweight or obese, and studies have shown that two thirds of ovarian cancer survivors are insufficiently active (10, 11). It has been hypothesised that obesity and inactivity negatively affect QoL through decreased physical endurance, limited mobility, associated comorbidities and possibly social discrimination (8). Interestingly, the associations between these factors and the QoL of ovarian cancer survivors has somehow been neglected in the current literature. We have recently published on the association between BMI and QoL, showing that increasing BMI is associated with poorer QoL outcomes in ovarian cancer (12). However, the association between physical activity (PA), BMI and QoL still remains unclear.

In order to accurately design and implement interventions to improve QoL, it is important to establish the role of BMI and PA in the QoL of ovarian cancer survivors. We have therefore evaluated the relationship between BMI, PA and the QoL of ovarian cancer survivors in a two-centre study.

Methods

Study population

This study was a two-centre cross-sectional study performed at the Royal Cornwall Hospital Trust (RCHT) and the Plymouth Hospitals NHS Trust (PHNT). Women who had undergone treatment for ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) between January 2007 and December 2014 were invited to participate by an invitation letter through the post. We excluded women who were under 18 years at time of study and who were diagnosed with borderline histology. Ethical approval was obtained through the Northampton Ethical committee and the study had full Trust approval at both sites.

Data collection

Women were identified through the cancer registry of the South West Intelligence Service which included their current status (alive versus deceased). Women were approached for participation through an invitation letter accompanied by an information leaflet, two questionnaires assessing QoL and PA, and an additional questions sheet covering current height and weight. Women were asked to return the completed questionnaires through a provided pre-paid envelope. After three weeks, a reminder was sent to women who did not reply to the initial survey.

Patient characteristics including age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status (13), disease stage, BMI at time of diagnosis, medical co-morbidities, current smoking status, treatment, the American Society of Anaesthesiologists (ASA) score, and recurrent disease were collected from medical records. BMI was calculated and categorised according to national guidelines; underweight (≤18.5 kg/m^2), normal range (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (≥30 kg/m^2) and morbidly obese (≥40 kg/m^2) (14). Incomplete data from respondents on their current weight and height were supplemented through review of medical files.

Physical activity was assessed by the validated Godin Leisure Time Questionnaire. This is a four-item questionnaire assessing the amount of mild, moderate and strenuous activity per 15 minutes in the past week. Frequency scores of moderate and strenuous activity were multiplied with corresponding Metabolic Equivalent (MET) values, assigning each patient a leisure score index (LSI) (15, 16). Women reporting moderate-to-strenuous LSI ≥24 were classified as active, whereas individuals reporting moderate-to-strenuous LSI ≤23 were classified as insufficiently active in accordance with public health guidelines (16-19). Women who did not report any moderate-to-strenuous exercise (LSI=0) were classified as sedentary.

Outcome measures

Quality of life was assessed through the validated European Organisation of Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-OV28 questionnaires (20, 21). The QLQ-C30 is a 30-item cancer-specific questionnaire, covering several areas of QoL; physical, role, emotional, cognitive and social functioning, as well as symptom distress and global QoL (20). A higher score on the functioning scales and global health represents a higher level of functioning and a higher QoL, while in symptom scales a higher score indicates a higher level of symptomatology (22). The QLQ-OV28 is a specific ovarian cancer module, covering specifically relevant issues such as body image, sexuality and abdominal symptoms (21).

Statistical analysis

Data were analysed using IBM SPSS software (23). For analysis purposes, BMI was categorized into; <25 kg/m^2 (normal), 25-29.9 kg/m^2 (overweight) or ≥30 kg/m^2 (obese). PA was categorised into 'sufficient', 'insufficient' or 'sedentary' following LSI scores. Reported outcomes of the QLQ-C30 and OV28 were linearly transformed to 0-100 scores (21, 22). Data were compared using the Pearson Chi square or Fisher's exact test for categorical data, and the Mann-Whitney U test, Kruskal-Wallis test or Median test for continuous data. The associations between current BMI, PA, and QoL outcomes were analysed using univariate analyses, and where appropriate multiple regression analyses were performed while adjusting for other factors including age, ECOG status, comorbidities, ASA score, stage, recurrent disease and time since diagnosis. P-values were regarded significant if <0.05 and the tests were two-sided.

Results

In total, 293 women who received treatment for ovarian cancer between January 2007 and December 2014 at the RCHT and PHNT were alive at time of study. Of the women invited to participate, 209 women (71.3%) completed the questionnaires. Five women did not fill in their current BMI and PA level. Consequently, outcomes of 204 women were available for analysis.

The median age of the study population was 63 years at diagnosis (range 17 - 87), and 48.8% had been diagnosed with stage I/II disease. The average time since primary diagnosis was 35 months (range 1-189). Almost all women had undergone surgery (97.1%) and received chemotherapy (83.7%) as part of their treatment. Non-respondents did not show different baseline and clinical characteristics compared to respondents including ECOG status (P=0.802), stage of disease (P=0.341) and operation (P=0.095). However, there was a significant difference in BMI at time of diagnosis (P=0.003), with non-respondents having higher average BMI (29.3 kg/m^2) compared to respondents (26.7 kg/m^2).

At the time of our survey, 91 women (46.7%) had a BMI below 25 kg/m^2, 69 women (35.4%) were overweight (BMI 25-29.9 kg/m^2) and 35 women (17.9%) were obese (BMI ≥30 kg/m^2), of which three were morbidly obese (BMI ≥40 kg/m^2). Fourteen women did not fill in their current weight. PA data were available for 202 women, of which only 42 women (20.8%) met the national guidelines for PA. The remaining 160 women (79.2%) were insufficiently active of which 51 women (25.2%) reported some PA, and 109 women (54.0%) reported a sedentary lifestyle.

Baseline and clinical characteristics did not differ significantly according to BMI groups (Table 1). Obese women had more comorbidities and poorer ECOG performance status compared to the normal weight and overweight, but this did not

Table 1 Baseline characteristics according to BMI categories

	BMI < 25 kg/m² N=91		BMI 25-29.9 kg/m² N=69		BMI ≥ 30 kg/m² N=35		Analysis P-value
Age at diagnosis							0.881
Median (range)	63	(21 - 87)	65	(25 - 83)	63	(17 - 81)	
Marital status							0.245
Married	62	(68.1%)	36	(52.5%)	22	(62.9%)	
Not married	8	(8.8%)	15	(21.7%)	4	(11.4%)	
Widow	4	(4.4%)	3	(4.3%)	3	(8.6%)	
Unknown	17	(18.7%)	15	(21.7%)	6	(17.1%)	
Smoking status							0.574
Yes	4	(4.4%)	5	(7.2%)	3	(8.3%)	
No	87	(95.6%)	64	(92.8%)	32	(91.4%)	
Co-morbidities							0.113
None	32	(35.2%)	19	(27.5%)	11	(31.4%)	
One	32	(35.2%)	28	(40.6%)	6	(17.1%)	
Two or more	26	(28.6%)	21	(30.4%)	18	(51.4%)	
Unknown	1	(1.1%)	1	(1.4%)	0	(0%)	
ECOG performance status							0.080
0	73	(80.2%)	57	(82.6%)	22	(62.9%)	
1	8	(8.8%)	7	(10.1%)	8	(22.9%)	
2-4	4	(4.4%)	3	(4.3%)	0	(0%)	
Unknown	6	(6.6%)	2	(2.9%)	5	(14.3%)	
FIGO stage							0.656
I-II	44	(48.4%)	34	(49.3%)	18	(51.4%)	
III-IV	44	(48.4%)	35	(50.7%)	16	(45.7%)	
Unknown	3	(3.3%)	0	(0%)	1	(2.9%)	
Surgery							0.571
Yes	87	(95.6%)	67	(97.1%)	35	(100%)	
No	4	(4.4%)	2	(2.9%)	0	(0%)	
ASA status							0.414
1	25	(28.7%)	13	(19.4%)	5	(14.3%)	
2	41	(47.1%)	38	(56.7%)	22	(62.9%)	
3	11	(12.6%)	11	(16.4%)	6	(17.1%)	
4	0	(0%)	1	(1.5%)	0	(0%)	
Unknown	10	(11.5%)	4	(6.0%)	2	(5.7%)	
Chemotherapy							0.789
Yes	74	(81.3%)	59	(85.5%)	30	(85.7%)	
No	17	(18.7%)	10	(14.5%)	5	(14.3%)	
Radiotherapy							0.883
Yes	4	(4.4%)	2	(2.9%)	1	(2.9%)	
No	87	(95.6%)	67	(97.1%)	34	(97.1%)	

Table 1 Continued

	BMI < 25 kg/m² N=91		BMI 25-29.9 kg/m² N=69		BMI ≥ 30 kg/m² N=35		Analysis P-value
Recurrence							0.776
Yes	23	(25.3%)	18	(26.1%)	11	(31.4%)	
No	68	(74.7%)	51	(73.9%)	24	(68.6%)	
Months since diagnosis							0.719
Median (range)	34	(2 – 189)	36	(1 – 114)	34	(4 – 116)	
Physical activity							0.012*
Sufficient	23	(25.3%)	13	(18.8%)	6	(17.1%)	
Insufficient							
Some activity	26	(28.6%)	20	(29.0%)	2	(5.7%)	
Sedentary	42	(46.2%)	35	(50.7%)	26	(74.3%)	
Unknown	0	(0%)	1	(1.4%)	1	(2.9%)	

*: P<0.05

reach statistical significance. At time of study, 72.7% of women had no evidence of recurrent disease. When comparing BMI at time of survey to BMI at diagnosis, 72.6% of women remained in the same BMI category while 27.4% changed, with 10.2% of women having a higher BMI category at time of survey and 17.2% a lower BMI category. PA levels varied significantly among BMI groups (P=0.012). In the BMI <25 kg/m² group, 25% of women was sufficiently active, while this was 19% in the overweight group and 17% in the obese group. Seventy-four percent of women in the obese group were sedentary as they reported no moderate or strenuous activity, while the normal and overweight group reported sedentary rates of 46% and 51% respectively.

BMI and quality of life

Obese women reported significantly poorer outcomes in terms of global QoL (P=0.008), physical (P=0.003), cognitive and social functioning (P=0.011, P=0.029) after adjustment for age, ECOG status, comorbidities, stage, recurrent disease and time since diagnosis (Table 2). In addition, obese women reported a poorer body image (P=0.023), and experienced significantly more fatigue (P=0.034), neurological symptoms (P=0.046), and chemotherapy side-effects (P=0.035) when compared to women with normal weight and overweight. Significantly poorer physical functioning was present in overweight women (BMI 25-29.9 kg/m²) when compared to women with a normal weight (P=0.026). After adjustment for PA levels, BMI still remained significantly associated with poorer QoL outcomes including global QoL (P=0.022), physical and cognitive functioning (P=0.014, P=0.012), body image (P=0.016) and fatigue (P=0.043) (Table 2).

Table 2 Quality of life outcomes according to BMI categories

	BMI < 25 kg/m² N=91	BMI 25-29.9 kg/m² N=69	BMI ≥ 30 kg/m² N=35	Univariate analysis	Multiple regression analysis[1]	Multiple regression analysis[2]
	Mean (SD)			P-value	P-value	P-value
QLQ-C30						
Global QoL	75.2 (20.5)	68.6 (21.5)	63.7 (21.2)	0.011*	0.008*	0.022*
Functioning scales						
Physical functioning	83.8 (21.0)	78.2 (21.2)	70.4 (24.8)	0.005*	0.003*	0.014*
Role functioning	78.0 (27.8)	73.1 (31.7)	69.1 (33.9)	0.417	NS	NS
Emotional functioning	82.7 (21.4)	80.1 (24.5)	77.9 (21.7)	0.349	NS	NS
Cognitive functioning	84.5 (19.3)	82.3 (21.5)	72.2 (25.9)	0.025*	0.011*	0.012*
Social functioning	83.3 (25.3)	76.4 (28.9)	71.1 (31.1)	0.036*	0.029*	NS
Symptom distress						
Fatigue	27.0 (23.2)	31.6 (24.0)	38.9 (27.7)	0.061	0.034*	0.043*
Nausea and vomiting	6.6 (16.8)	9.2 (20.9)	9.0 (14.2)	0.116	NS	NS
Pain	15.9 (22.6)	20.3 (27.4)	25.2 (29.8)	0.264	NS	NS
Dyspnoea	14.3 (24.9)	19.6 (27.2)	21.9 (25.5)	0.099	NS	NS
Insomnia	30.7 (33.2)	34.2 (31.8)	31.4 (29.1)	0.661	NS	NS
Appetite loss	12.1 (27.4)	15.0 (28.3)	14.3 (23.3)	0.344	NS	NS
Constipation	14.7 (23.4)	15.9 (26.6)	21.9 (30.2)	0.489	NS	NS
Diarrhoea	9.1 (22.4)	10.9 (20.4)	10.8 (22.8)	0.499	NS	NS
Financial difficulties	8.6 (23.3)	16.2 (32.2)	12.7 (27.2)	0.318	NS	NS

QLQ-OV28								
Functioning								
Body image	77.2	(26.5)	67.9	(29.1)	66.7	(31.8)	0.051	0.023*	0.016*
Sexual functioning	17.6	(22.6)	12.4	(22.4)	10.8	(18.9)	0.179	NS	NS
Attitude to disease	67.7	(27.5)	60.2	(26.7)	58.8	(28.5)	0.106	NS	0.035*
Symptom distress								
Abdominal symptoms	18.8	(20.2)	22.1	(19.8)	25.3	(19.2)	0.057	NS	NS
Neurological symptoms	26.5	(28.2)	26.7	(30.8)	41.0	(33.2)	0.065	0.046*	NS
Menopausal symptoms	26.1	(30.8)	21.4	(27.6)	23.8	(26.3)	0.715	NS	NS
Other chemotherapy side-effects	23.7	(18.0)	26.2	(20.8)	33.2	(20.2)	0.057	0.035*	NS

1: Corrected for age, ECOG status, comorbidities, stage, recurrent disease and time since diagnosis; 2: Corrected for age, ECOG status, comorbidities, ASA, stage, recurrent disease, time since diagnosis and physical activity; *: $P<0.05$; NS: not significant

Table 3 Quality of life outcomes according to physical activity

	Sufficient N=42	Insufficient N=51	Sedentary N=109	Univariate analysis	Multiple regression analysis[1]	Multiple regression analysis[2]
	Mean (SD)			P-value	P-value	P-value
QLQ-C30						
Global QoL	79.6 (18.3)	74.0 (19.8)	66.7 (21.7)	0.002*	<0.001*	0.005*
Functioning scales						
Physical functioning	91.2 (9.3)	89.0 (13.5)	71.0 (24.6)	<0.001*	<0.001*	<0.001*
Role functioning	86.5 (18.9)	81.7 (26.7)	67.1 (32.9)	0.001*	<0.001*	<0.001*
Emotional functioning	84.5 (19.8)	79.6 (23.6)	79.8 (22.8)	0.485	NS	NS
Cognitive functioning	84.1 (20.1)	82.7 (17.0)	79.8 (23.5)	0.639	NS	NS
Social functioning	88.1 (22.2)	82.3 (26.7)	73.5 (29.7)	0.003*	<0.001*	<0.001*
Symptom distress						
Fatigue	22.5 (20.2)	23.4 (19.4)	36.6 (26.8)	0.001*	<0.001*	<0.001*
Nausea and vomiting	4.0 (9.6)	5.2 (14.3)	10.2 (19.8)	0.026*	0.024*	0.041*
Pain	9.5 (15.7)	16.7 (23.1)	23.7 (29.2)	0.028*	<0.001*	<0.001*
Dyspnoea	9.5 (16.9)	12.4 (24.0)	22.5 (28.0)	0.003*	0.006*	0.017*
Insomnia	26.2 (28.1)	27.5 (28.8)	37.0 (34.2)	0.125	NS	NS
Appetite loss	6.3 (19.8)	7.8 (15.8)	18.3 (31.6)	0.026*	0.006*	0.009*
Constipation	15.9 (26.8)	11.1 (19.6)	18.8 (27.8)	0.265	NS	NS
Diarrhoea	4.0 (10.9)	8.2 (16.0)	13.1 (26.0)	0.136	0.017*	0.021*
Financial difficulties	14.3 (27.7)	11.1 (26.9)	10.8 (25.9)	0.427	NS	NS

QLQ-OV28						
Functioning						
Body Image	75.4 (24.5)	73.8 (30.0)	69.4 (30.0)	0.538	0.018*	NS
Sexual functioning	24.8 (28.7)	19.4 (21.0)	8.4 (15.8)	<0.001*	0.001*	<0.001*
Attitude to disease	63.8 (30.8)	66.2 (26.7)	62.0 (27.3)	0.638	NS	NS
Symptom distress						
Abdominal symptoms	15.1 (18.5)	20.0 (18.9)	24.0 (21.2)	0.020*	0.023*	0.035*
Neurological symptoms	15.1 (22.1)	20.5 (23.8)	39.1 (32.8)	<0.001*	<0.001*	<0.001*
Menopausal symptoms	25.8 (31.7)	26.8 (30.4)	21.9 (26.4)	0.663	NS	NS
Other chemotherapy side-effects	18.4 (18.8)	22.5 (16.5)	31.4 (19.7)	<0.001*	<0.001*	<0.001*

1: Corrected for age, ECOG status, comorbidities, ASA, stage, recurrent disease and time since diagnosis; 2: Corrected for age, ECOG status, comorbidities, ASA, stage, recurrent disease, time since diagnosis, and BMI; *: P<0.05; NS: not significant

Physical activity and quality of life

Baseline and clinical characteristics did not differ among PA groups, except for ECOG status (P=0.020) and ASA score (P<0.001). A higher number of women who were sedentary had a poorer ECOG score compared to the other two groups, and this was similar for ASA scores (data not shown).

After adjustment for possible confounding factors, global QoL was significantly worse in women who were insufficiently active (P<0.001), with the poorest QoL being reported among sedentary women (Table 3). Women who were sedentary reported significantly poorer physical (P<0.001), role (P<0.001) and social functioning (P<0.001). In terms of symptom distress, sedentary women reported more fatigue (P<0.001), nausea and vomiting (P=0.024), pain (P<0.001), dyspnoea (P=0.006), appetite loss (P=0.006) and diarrhoea (P=0.017). In addition, sedentary women had a poorer body image (P=0.018) and sexual functioning (P=0.001), more abdominal and neurological symptoms (P=0.023 and P<0.001) and more chemotherapy side-effects (P<0.001). These deteriorations in QoL outcomes remained significant after adjustment for BMI, except for body image (Table 3).

Insufficiently active women who were still active to some extent reported significantly better QoL in terms of global QoL, physical, role and social functioning and less symptom distress when compared the sedentary group (data not shown).

BMI, physical activity and quality of life

BMI and PA are both independently associated with poorer QoL outcomes. However, PA is associated with more QoL outcomes including more functioning domains and symptom distress scores compared to BMI (Table 2, Table 3). Within every BMI category, we looked at subgroups based on PA levels. There was an additional effect of PA within every BMI category, with lower scores in women reporting lower PA levels for the majority of functioning and symptom distress scales (data not shown).

When looking specifically at obese women who were sedentary, these women had the poorest outcomes in almost all functioning domains, with average scores of; global QoL 60.0, physical functioning 64.7, role functioning 65.4, emotional functioning 75.0, cognitive functioning 70.0, social functioning 65.3, and sexual functioning 8.3.

Discussion

The number of ovarian cancer survivors is increasing; making survivorship issues such as QoL an important component of their care. Over the past 15 years, the percentage of the general population being either overweight or obese has risen to 57% in the United Kingdom (14). Increased BMI has been linked to an enhanced risk of ovarian cancer, and as this epidemic shows no signs of abating, its impact on the outcomes of cancer patients has become a primary focus of research (24). In this study, we assessed the association between BMI, PA and the QoL of ovarian cancer survivors.

In our study, 35.4% of the women were overweight and 17.9% were obese at the time of the survey, which is consistent with national reported rates (14). Only 20.8% of our population met the recommendations for PA, which is far less than the national average of 55% and previously reported numbers of 31.1% for ovarian cancer survivors (11, 14).

So far there have been few studies addressing the effect of BMI on the QoL of ovarian cancer survivors. We recently published that increasing BMI is associated with poorer QoL outcomes in terms of physical functioning (12). In the current study, we confirm the detrimental association between increasing BMI and QoL outcomes, showing that obesity is associated with multiple poorer QoL outcomes of ovarian cancer survivors including global QoL, physical, cognitive, and social functioning. The significant association between BMI and QoL persisted after controlling for PA levels.

In addition, we found that significant poorer physical functioning is already present in survivors who are overweight (BMI 25-29.9 kg/m^2). This is a novel finding, as most studies described an effect occurring at a BMI level of ≥30 kg/m^2, which may imply that poorer physical functioning is present at a lower BMI than is generally assumed (25-28). Furthermore, we found that obese women report more symptomatology, including fatigue and neurological symptoms, which has been reported by previous studies (28, 29). In addition, obese women reported more chemotherapy side-effects. This is contradictory to results of a recent review stating that obese women do not experience more toxicities compared to normal-weight individuals (30). Moreover, the review suggested that obese women are at increased risk of receiving sub-optimal dosages following unfounded concerns about increased toxicities (30).

Studies among endometrial cancer survivors confirm our findings, stating that obese women report a poorer QoL including worse physical, social and role functioning, and more symptom distress (7, 25-28, 31). In addition, these negative effects of increasing BMI on QoL have also been described in the general population (32).

In our study, ovarian cancer survivors who do not meet the guidelines for PA reported significantly poorer QoL. This included global QoL, physical, role, social and sexual functioning. In addition, they reported significantly more symptom distress in the majority of scales assessed. Women reporting sedentary levels of PA had the poorest QoL outcomes and the highest symptomatology, and their outcomes were significantly poorer compared to other insufficiently active women who were still active to some extent.

Our results are supported by previous studies, stating that ovarian cancer survivors who do not meet the recommendations for PA have a poorer QoL (11, 33, 34). Stevinson et al. reported that ovarian cancer survivors who do not meet the guidelines for PA scored significantly lower on global QoL and physical, functional, emotional well-being and had more symptom distress (11, 34). However, they found no difference in QoL between women who do not meet the guidelines and women who are sedentary (11). Our study did show a significant difference between insufficiently active and sedentary women in QoL outcomes and symptom distress. We therefore hypothesise that being active to some extent, even though insufficiently, may improve QoL as opposed to being sedentary.

This hypothesis is strengthened by our results showing that within every BMI category, lower PA was associated with poorer QoL. This suggests a cumulative detrimental effect of a high BMI and sedentary behaviour, with obese sedentary women having the poorest QoL outcomes and highest symptom distress of the whole study population.

We show that both a high BMI and insufficient PA are independently associated with poorer QoL. Interestingly, PA affected more QoL domains, including role and social functioning and more symptomatology. Both factors need to be addressed in survivorship programmes to evaluate if QoL outcomes of ovarian cancer survivors can be modified. Thus far, few interventional studies addressing lifestyle have been undertaken in ovarian cancer patients, but have been deemed feasible during active treatment and post-treatment (35-37). Newton et al. assessed a walking intervention in patients undergoing chemotherapy, and found it was feasible, acceptable and safe, with meaningful improvements in QoL (35-37). In addition, von Gruenigen et al. reported that a lifestyle intervention consisting of PA and nutrition counselling in ovarian cancer patients is feasible, and improved QoL (36). Another study evaluated exercise and health education after completion of treatment, and found significant improvements in cardiopulmonary function and QoL (37). Other studies among gynaecological cancer patients also confirm the feasibility and value of lifestyle interventions in improving QoL (38, 39).

Future efforts should focus on developing lifestyle interventions to improve the outcomes of this patient group. We suggest that these interventions should incorporate the promotion of PA and weight loss, as both play significant role in the

QoL of survivors and are associated with different aspects of QoL and symptomatology. Moreover, high BMI and insufficient PA have both been implicated to negatively affect disease-specific survival and overall survival in ovarian cancer patients (40-43). Preliminary evidence suggests that weight loss and increasing PA may positively influence biomarkers associated with survival (43-45). Lifestyle interventions may therefore improve survival outcomes in addition to QoL.

Important strengths of the study are the two-centre design and the use of validated questionnaires to measure QoL and PA. Third, we used BMI at time of survey as opposed to using BMI at diagnosis, as our data revealed that the BMI changes over time. In addition, our response rate was 71.3% and we compared characteristics of respondents to non-respondents, which showed no significant differences in the majority of characteristics.

Non-respondents had a higher BMI at time of diagnosis, limiting the representativeness of our results. Other limitations are the relatively small study population and the geographical setting. The number of women who meet the national guidelines for PA is smaller than previously reported numbers (11, 33). However, our relatively small number of sufficiently active women does demonstrate the current situation and the need for interventions to tackle this important health issue. Most ovarian cancer patients are diagnosed with advanced stage (III/IV) disease, however the majority of our study population comprised of stage I/II disease consistent with reported survival rates (3). Therefore our results may not be representative for the whole population of ovarian cancer patients, but are a depiction of women surviving ovarian cancer.

Self-reported weight, height and PA levels were used to assess associations with QoL, as recent evidence shows that these measures are accurate in cancer patients and older adults (16, 46). However, we recognise the limitations of self-reported measures and therefore recommend the use of objective measures in future prospective studies.

Conclusion

Our study shows that BMI and PA are significantly associated with the QoL of ovarian cancer survivors, with obese and sedentary survivors reporting significantly poorer QoL. Future efforts should be directed at assessing lifestyle interventions promoting both exercise and weight loss as possible means to modify lifestyle, and consequently the QoL of ovarian cancer survivors.

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8

Future directions


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9

THE EFFECT OF LIFESTYLE INTERVENTIONS ON THE QUALITY OF LIFE OF GYNAECOLOGICAL CANCER SURVIVORS: A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract

Objectives

We aimed to evaluate the effectiveness of lifestyle interventions in improving the quality of life (QoL) of endometrial and ovarian cancer survivors.

Methods

The review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, and the Cochrane Handbook for Systematic Reviews of Interventions. We performed a search of Medline (1946-2015), Embase (1980-2015), Cinahl (1981-2015), PsycInfo (1806-2015) and the Cochrane Trial Register to identify studies evaluating the effect of lifestyle interventions on the QoL of endometrial and ovarian cancer survivors.

Results

Eight studies fulfilled the inclusion criteria and comprised a total of 413 patients. Three studies were randomised controlled trials (RCTs), which showed that lifestyle interventions may improve physical functioning and significantly reduce fatigue in endometrial cancer survivors. In addition, lifestyle interventions in endometrial cancer survivors resulted in significant weight loss and improved physical activity levels, but did not show improvements in global QoL in the meta-analysis ($P=0.75$, $P=0.49$). Non-randomised trials in ovarian cancer survivors support the feasibility of lifestyle interventions and suggest they may result in QoL improvements.

Authors' Conclusions

Lifestyle interventions have the potential to improve the QoL of endometrial and ovarian cancer survivors, and may significantly reduce fatigue. However, the current evidence is limited and there is a need for future studies to further evaluate lifestyle interventions and their effect on QoL outcomes.

Background

Gynaecological cancer accounts for about 1 in 10 of all cancers diagnosed in women, and the majority are diagnosed with endometrial cancer or ovarian cancer (1). Over the past years there have been great advances in treatment and consequently improved survival (2, 3). This has led to an increase in the number of survivors, making survivorship programmes an important and integral part of patients' care.

Survivors experience poorer health-related quality of life (QoL) compared to the general population, with physical and psychological sequelae following cancer diagnosis and its treatment (4, 5). These poorer outcomes have been linked to physical activity levels, body mass index (BMI), and other lifestyle factors (6-9). Currently, the majority of endometrial and ovarian cancer survivors do not meet public recommendations for exercise and nutrition, with many engaging in a sedentary lifestyle (9, 10). In addition, the majority of women are overweight or obese, and experience several obesity-related comorbidities (7, 10, 11). Consequently, endometrial and ovarian cancer survivors are particularly at risk of impaired QoL.

Strategies aiming to improve QoL have received increasing interest over the past years. A recent Cochrane review indicated that exercise may have beneficial effects on QoL in cancer survivors (12). However, despite the ample evidence in other cancer sites such as breast cancer, there is limited evidence regarding the effectiveness of lifestyle interventions in improving the QoL of gynaecological cancer survivors (12).

Therefore, our aim in this systematic review is to evaluate the effectiveness of lifestyle interventions in improving the QoL of endometrial and ovarian cancer survivors.

Methods

Criteria for considering studies for this review

This review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (13), and in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions (14). Studies evaluating lifestyle interventions for endometrial and ovarian cancer survivors were identified. Eligible study designs included; randomised controlled trials (RCTs), controlled clinical trials, pilot studies and feasibility studies.

Types of participants

- Adult women (age ≥18 years) diagnosed with endometrial cancer having completed primary treatment (surgery, chemotherapy or radiotherapy).
- Adult women (age ≥18 years) diagnosed with ovarian cancer having completed primary treatment (surgery, chemotherapy or radiotherapy).

Types of interventions and outcome measures

Studies were included if they evaluated any type of lifestyle intervention in endometrial or ovarian cancer survivors. Outcome measures included all QoL outcomes measured using generic and cancer-site specific scales that have been validated through reporting of norms.

Search methods for identification of studies

The protocol was based on the PRISMA statement (13). A systematic search of studies evaluating lifestyle interventions in endometrial and ovarian cancer survivors was performed in Medline (1946 until July 2015), Embase (1980 until July 2015) Cinahl (1981 until July 2015), PsycInfo (1806 until July 2015) and the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register. The search strategy based on terms related to the review topic is presented in Appendix 1, and was adapted accordingly to each database. Furthermore, abstracts of scientific meetings and the reference lists of eligible studies were searched to identify any additional studies eligible for inclusion.

Data collection and analysis

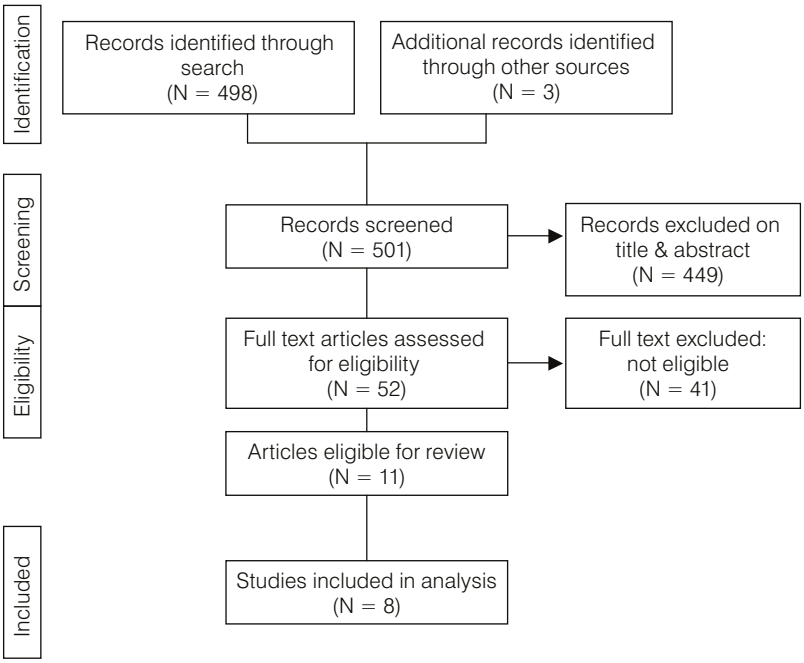
Two reviewers (AS and KG) independently assessed titles and abstracts of all identified studies. Studies that clearly did not meet the inclusion criteria were excluded. Potentially relevant studies were retrieved in full text, and were further reviewed for eligibility by both reviewers. Differences were resolved by discussion on appeal to a third review author (AL). We excluded studies where the majority of participants were undergoing active treatment for a primary cancer. The risk of bias instruments recommended by the Cochrane Studies Methods Group was used for randomised controlled trials and non-randomised comparative studies (15, 16). Outcome scales of QoL measures were compared across different studies in the meta-analysis where possible. The meta-analysis was performed using the random-effects model in the Cochrane Review Manager (RevMan) Software.

Results

Results of the search

The search strategy identified 382 references in Embase, 71 in Medline, 25 in Cinahl, 14 in PsycInfo and one Cochrane review (Figure 1). After reviewing title and abstracts, 46 articles were retrieved in full. The Cochrane review identified a further six studies which were retrieved in full. After full text screening, eight articles were eligible for this review. A search of the grey literature further identified three articles, resulting in the inclusion of 11 articles in this review, which comprised 8 unique studies.

Figure 1 PRISMA flow diagram of selection of studies



Included studies

A total of eight studies met the inclusion criteria and characteristics are illustrated in Table 1 and 2. Three studies were RCTs (17-22), one study was a randomised parallel intervention trial (23), one was a controlled trial (24), and three were single-arm intervention trials (25-27). Four trials included endometrial cancer survivors (17-21, 25, 26), three trials included ovarian cancer survivors (23, 24, 27), and one study

Table 1 Summary of included randomised controlled lifestyle intervention trials

Trial	Population	Intervention
Donnelly et al. 2011 (22)	33 gynaecological cancer patients (OC: 12, EC: 11), stage I-III Intervention: N=16 Control: N=17	12-week physical activity behavioural change intervention, home-based
McCarroll et al. 2014 (17, 21)	75 endometrial cancer survivors, stage I-II Intervention: N=41 Control: N=34	6-month behavioural physical activity and nutritional counselling on individual (3, 6 and 12 mo) and group basis (10 weekly and 6x biweekly)
Von Gruenigen et al. 2009 (18-20)	45 endometrial cancer survivors, stage I-II Intervention: N=23 Control: N=22	6-month behavioural physical activity and nutritional counselling (6x weekly, 2x biweekly, 3x monthly), home-based

CG: control group; IG: intervention group; mo: months; wks: weeks

evaluated a combination of gynaecological cancer patients (22). One trial also included breast cancer survivors (26). All studies combined comprised a total of 413 cancer survivors, including 255 endometrial cancer survivors and 122 ovarian cancer survivors.

Randomised controlled lifestyle intervention trials

Summary of lifestyle interventions

Three of the included studies were RCTs, evaluating home-based behavioural lifestyle interventions of exercise alone or a combination of exercise and nutrition, with one being partly hospital-based for group counselling sessions (Table 1). The duration varied from three to six months. Exercise included aerobic training, or a combination of aerobic and strength or resistance training. The majority included endometrial cancer patients, although Donnelly et al. also included twelve ovarian cancer patients, and other gynaecological cancer patients (uterine; N=4, cervical; N=4, mixed; N=2) (22). All trials evaluated QoL using the FACT-G questionnaire, and fatigue and depression were also assessed as part of QoL. Weight loss was included as an outcome in two trials (18, 21).

Outcome measures & time points	Results / conclusion
Fatigue (MFSI-SF & FACIT-F), QoL (FACT-G), depression (BDI-II), positive and negative affect (PANAS), body composition, physical functioning (12-min walk test), sleep dysfunction (PSQI) self-reported physical activity (7 day PAR) At baseline, 6, 12 wks and 6 mo	Significant improvement in fatigue, negative effect and sleep dysfunction in IG compared to CG. No difference in QoL, depression, physical activity, BMI and affect.
Weight loss, self-efficacy (WEL), QoL (FACT-G), physical activity, nutrient intake At baseline, 3, 6 and 12 mo	Significant improvement in physical functioning, fatigue and self-efficacy in IG compared to CG. Significant improvement in weight, physical activity and nutrition in IG compared to CG. Significant improvement of overall QoL in IG over time.
QoL (FACT-G, SF-36), fatigue (FACT-F) self-efficacy (WEL), eating behaviour (TFEQ), depression (BDI), anthropometrics (weight, waist circumference, BMI), physical activity, dietary intake At baseline, 3, 6, and 12 mo	Significant improvement in self-efficacy and social pressure in IG compared to CG. Significant improvement in weight, physical activity and nutrient intake in IG and compared to CG. No difference in QoL, fatigue and depression between groups.

Effects of lifestyle interventions on quality of life

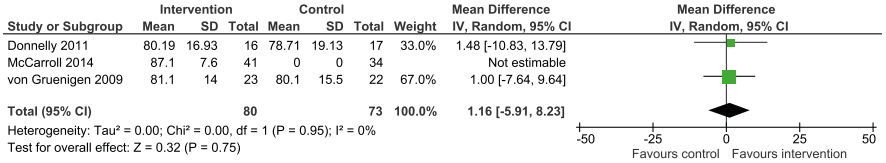
McCarroll et al. reported a significant improvement in global QoL in the intervention group over time (21). Fatigue improved significantly in the intervention group of two studies (21, 22), and physical functioning improved significantly in one trial (21). However, none of the trials reported a significant improvement in global QoL in the intervention group over the control group, and a meta-analysis of global QoL scores showed a non-significant mean difference of 1.16 (95% confidence interval (CI): -5.91 – 8.23, P=0.75) and 2.48 (95% CI: -4.63 – 9.58, P=0.49) at three months and six months respectively (Figure 2). McCarroll et al. only reported global QoL scores of the intervention group and could therefore not be estimated in the meta-analyses.

Von Gruenigen et al. failed to show a difference in fatigue and physical functioning between groups (18). No other QoL differences were found in the trials, and a meta-analysis of other outcomes could not be performed because of insufficient available data for individual QoL domains and symptom distress.

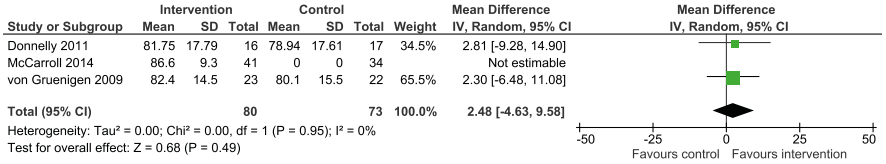
Self-efficacy was evaluated using the Weight Efficacy Lifestyle (WEL) questionnaire and certain aspects improved significantly among the intervention groups (18, 21). Furthermore, there was a significant decrease of sleep dysfunction in the intervention

Figure 2 Meta-analysis of global quality of life outcomes

Global quality of life at 3 months



Global quality of life at 6 months



group compared to the controls (22). Two studies assessed weight loss, and reported significant weight loss as a result of the intervention (18, 21). In addition, Von Gruenigen et al. showed a significant improvement in physical activity in the intervention group (17, 18). Depression was assessed by two trials using the Becks Depression Inventory (BDI), but showed no significant improvements associated with the interventions (18, 22).

Other lifestyle intervention studies

Summary of lifestyle interventions

Details of the remaining five non-randomised intervention studies are shown in Table 2. The majority assessed an exercise programme (24, 25, 27), one trial included an exercise and nutritional component (26), and one trial evaluated a dietary intervention only (23). The duration of the lifestyle interventions varied from four weeks to six months. The majority of interventions were delivered through counselling, with some studies incorporating a behavioural component (23, 27). The physical activity component included different exercise modes, including aerobic (25), aerobic and resistance training (26, 27), and a combination of aerobic, strength and flexibility training (24), and were unsupervised. Most exercise interventions aimed to meet the recommended physical guidelines of moderate-to-vigorous physical activity for 150 minutes per week (24-26). The dietary interventions encompassed nutritional counselling (26) or a diet (23). The setting of the trials was home-based (23-27).

Effect of lifestyle interventions on quality of life

Endometrial cancer

Two single-arm studies have been performed in endometrial cancer survivors (25, 26). Basen-Engquist et al. evaluated a 6-month exercise intervention in 100 survivors and reported significant improvements over time in several QoL outcomes and cardiorespiratory fitness (Table 2) (25). McCarroll et al. performed a single-arm feasibility study of a 4-week lifestyle intervention using an interactive mobile application, and deemed it feasible with improvements in BMI and self-efficacy, but did not demonstrate improvements in QoL at the end of the intervention (26).

Ovarian cancer

Three studies have been undertaken among ovarian cancer survivors, including a controlled trial, a parallel group trial and a pilot study. The controlled trial evaluated a 8-week exercise intervention combined with health education, and showed improved QoL including physical, social, emotional and functional wellbeing, and improved cardiopulmonary fitness in the intervention group (24). The pilot study showed increased physical fitness and decreased waist circumference after a 24-week exercise intervention, but did not find significant improvements in QoL, fatigue or other outcomes assessed (27). The parallel trial compared a low fat high fibre diet (LFHF) to a fruit and vegetable juice concentrate (FVJC), and supports the feasibility of dietary interventions for ovarian cancer survivors. They also reported an improved dietary intake in the LFHF group but found no significant weight change or QoL improvements (23).

Quality of study methods

Three of the included studies were RCTs, all other studies were non-randomised and the majority were single-arm intervention trials, leading to a high risk of bias associated with non-randomisation, patient attrition, and selective reporting. Following the nature of the intervention, it may pose difficulties to blind participants to the intervention delivery. However, blinding of outcome assessors was only reported in one RCT, and none of the other controlled trials. With regards to confounding factors, only two RCTs corrected for possible confounders in their statistical analysis. There was a large heterogeneity among studies regarding the selection of patients in terms of stage and inclusion criteria. Studies included different cancer sites as well as different stages of disease ranging from early stage (I/II) to all stage disease. Two RCT's only included overweight women (BMI ≥ 25 kg/m^2) and the other RCT only included sedentary women with mild to severe fatigue, resulting in a considerable selection bias. Three studies did not exclude women based on BMI or physical activity levels (23, 25, 27). Furthermore, some trials included both women undergoing active treatment and women having completed treatment (22, 27).

Table 2 Summary of non-randomised / single-arm lifestyle intervention studies

Study	Study design	Participants	Intervention
Endometrial cancer			
Basen-Engquist et al. 2014 (25)	Single-arm intervention study	100 endometrial cancer survivors, stage I-IIIa	6-month exercise (walking) intervention, home-based, 30 min/day moderate-intensity ≥5x/week
McCarroll et al. 2015 (26)	Single-arm feasibility trial	19 endometrial cancer survivors, 26 breast cancer survivors, 5 endometrial + breast cancer survivors, stage I-II BMI ≥25	4-week exercise and nutritional intervention through interactive mobile application, home-based
Ovarian cancer			
Hwang et al. 2014 (24)	Controlled trial	40 ovarian cancer survivors, stage I-III Insufficient physical activity	8-week group education and self-help (weekly) and home-based exercise intervention
Moonsammy et al. 2013 (27)	Single-arm pilot study	19 ovarian cancer patients, 7 undergoing adjuvant treatment, 12 survivors, stage I-III	6-month exercise and cognitive behavioural intervention, home-based
Paxton et al. 2012 (23)	Randomised non-controlled parallel intervention trial	51 ovarian cancer survivors, stage II-IV	6-month dietary intervention (LFHF diet or FVJC diet), home-based, 8 weekly, 4 biweekly, 2 monthly

CG: control group; FVJC: fruit and vegetable juice concentrate; IG: intervention group; LFHF: low fat high fibre; mo: months; wks: weeks

Outcome measures & time points	Results / conclusion
Exercise minutes, anthropometrics and fitness At baseline, 2, 4 and 6 mo QoL (SF36 & QLACS) and psychological distress (BSI-18 & PSS) At baseline and 6 mo	Significant improvement in physical activity, waist circumference, and QoL including; physical functioning, perceived general health, vitality, mental health, negative and positive feelings, cognitive problems, pain, sexual problems, fatigue, social avoidance, perceived benefits and recurrence distress. Non-obese had significantly better outcomes in some QoL domains compared to obese.
Weight change, feasibility outcomes, QoL (FACT-G), self-efficacy (WEL), physical activity, daily food intake, anthropometrics (waist circumference) At baseline and 4 wks	Improvement of weight, BMI, waist circumference and self-efficacy. No difference in QoL.
Cardiopulmonary function (12-min walk test), muscle strength, immune response, QoL (FACT-G) At baseline and 8 wks	Improvement of cardiopulmonary fitness, muscle strength and QoL including, physical, social, emotional and functional wellbeing in IG compared to CG.
QoL (FACT-O), fatigue (FACIT-Fatigue), effects of endocrine treatment (FACT-ES), vigour and mood (POMS-SF-V), peripheral neuropathy (FACT-GOG/NTX), depression (CES-D), anxiety (STAI-Y), post-traumatic stress symptomology (PCL-C), self-efficacy (CBI-B), physical activity (GLTI), aerobic capacity, body fat percentage, waist circumference At baseline, 12 and 24 wks	Significant improvements in aerobic capacity and waist circumference. No difference in QoL.
Serum carotenoid and alpha-tocopherol levels, dietary intake, QoL (SF-36), weight, waist-to-hip ratio, QoL, albumin, CA125, feasibility outcomes At baseline and 6 mo	Significant improvements in carotenoid and alpha-tocopherol levels in both groups. Improvement in dietary intake in LFHF group. No difference in QoL or weight.

Discussion

Quality of life impairment is a significant issue among cancer survivors, but may be reversible through modifiable factors such as physical activity levels and weight. Within gynaecological oncology, lifestyle interventions are not widely adopted, despite this group being known for their unhealthy lifestyle (10). With this review, we aimed to give a detailed overview of the current literature evaluating the effectiveness of lifestyle interventions in improving the QoL of endometrial and ovarian cancer survivors.

We found that within endometrial cancer survivors, lifestyle interventions may improve physical functioning and significantly reduce fatigue, as well as have a positive effect on self-efficacy and sleep dysfunction. Furthermore, lifestyle interventions incorporating physical activity and nutrition resulted in significant weight loss and improved physical activity levels. The largest single-arm intervention study showed significant improvements in multiple QoL domains over time. However, we did not find an improvement in global QoL or other QoL outcomes in the RCTs.

Among ovarian cancer survivors, lifestyle interventions have not yet been evaluated in a randomised controlled setting. However, preliminary non-randomised studies have shown promising results, supporting the feasibility of both exercise interventions and dietary interventions. Weight loss and improved physical fitness are also achievable, and may result in QoL improvements.

When looking at results from other cancer sites, Mishra et al. evaluated the effect of exercise on QoL of various cancer survivors who completed active treatment in a Cochrane review (12). They found that exercise has a positive impact on global QoL and QoL domains including emotional, social and sexual functioning. Furthermore, exercise interventions resulted in decreased fatigue, pain and anxiety. However, no conclusion could be drawn regarding the effect of exercise on physical, cognitive and role functioning (12). Another review also supports the beneficial effects of exercise on general health and QoL outcomes in cancer survivors, and stated that dietary interventions improve body weight and diet quality (28).

Although these findings generally concur with the findings of our review regarding the beneficial effects of lifestyle interventions and their feasibility in the endometrial and ovarian cancer survivor population, there are still some discrepancies in terms of effect on QoL outcomes. We believe that this may be an effect of the limited number of studies and the small study populations of the included trials in this review. Despite the optimistic results, future studies are needed to establish which QoL outcomes and to what extent these outcomes can be modified within this population.

In addition, the majority of the studies assessed unsupervised, home-based interventions. Although this mode of delivery is convenient and economically attractive, it is unclear whether this will result in optimal lifestyle improvements. A recent Cochrane review concluded that interventions promoting exercise in cancer

survivors should involve setting programme goals, prompting practise and self-monitoring, and encouraging participants to attempt to generalise behaviours learned in supervised exercise environments to achieve optimal effectiveness (29). Therefore, possible alternatives such as supervised individual and group sessions need to be explored, and should also include settings other than home-based. Group sessions may be an especially attractive alternative, as they may also function as a means of social and psychological support. Furthermore, some studies had variable components of interventions and included multimodal programmes or single mode programmes of exercise or nutrition alone. As both programmes resulted in significant changes in quality of life outcomes, future studies should further evaluate which components are essential for optimal quality of life improvements.

Currently, there is also a lack of evidence regarding the sustainability of lifestyle changes induced by these short-term interventions. It is imperative to understand which interventions are most efficacious in supporting long-term healthy lifestyle behaviour, especially as there is emerging evidence that physical activity and weight influence cancer survival (29-32).

Overall completeness and applicability of the evidence

This review analysed eight studies, including three RCTs. The studies included both endometrial and ovarian cancer patients of which almost all had completed primary treatment. The majority of endometrial cancer survivors included were diagnosed with early stage disease, consistent with reported rates, and for the ovarian cancer studies all stages were included (33). Socio-demographic characteristics were described in most studies and comprised a predominantly white population, which may limit the applicability to a broader population. In addition, there was significant variation in lifestyle interventions in terms of components, mode, duration and frequency, and considerable selection bias of overweight and inactive survivors. Furthermore, the long-term sustainability and effects have not been addressed. The majority of outcomes could not be compared in the meta-analysis because of insufficient data on individual QoL domains or symptom distress. We contacted the corresponding authors of two papers for additional data, but received no response.

Quality of evidence

The results of our review are preliminary following the limited available evidence and should therefore be interpreted with caution. The majority of studies were susceptible to a high risk of bias, mainly because of their non-randomised or single-arm design, and most studies did not adjust for possible confounding factors. All studies used internationally validated QoL questionnaires and outcomes were comparable across studies. Well-designed future studies are therefore recommended to further assess lifestyle interventions as a means to improve health behaviour and QoL.

Potential biases in review process

We performed a comprehensive search of the literature, which was performed by two reviewers (AS and KG), and included a search of the grey literature. A language resection was applied to the search to only include English papers. Both reviewers assessed potentially eligible articles independently, and differences were resolved by appeal to a third reviewer (AL).

Future studies

There is a need for further lifestyle intervention studies in the gynaecological cancer population to determine its exact effect on QoL outcomes. Ideally, these will be performed in a randomised controlled setting, and should include women regardless of their BMI and physical activity levels. Essential attributes of the interventions in terms of components, delivery mode, frequency and duration need to be further explored to establish optimal effectiveness. Future studies should consider assessing supervised interventions in settings other than home-based. Furthermore, the sustainability of lifestyle changes and QoL improvements need to be evaluated on a long-term basis, and whether they will translate in a survival benefit.

Conclusion

Lifestyle interventions have the potential to improve the QoL, and significantly reduce symptom distress such as fatigue in endometrial cancer and ovarian cancer survivors. However, the current evidence is limited, and there is a need for future studies further evaluating lifestyle intervention and their effect on QoL outcomes. Essential attributes of lifestyle interventions still remain unclear and need to be explored to establish optimal effectiveness and long-term sustainability.

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Appendix 1 – Search strategy

1. ENDOMETRIUM CANCER
2. endometr* cancer
3. uter* cancer
4. endometr* neoplasm
5. uter* neoplasm
6. endometr* carcinoma
7. uter* carcinoma
8. OVARY CANCER
9. ovar* cancer
10. ovar* neoplasm
11. ovar* tumour
12. ovar* tumor
13. GYNECOLOGIC CANCER OR FEMALE GENITAL TRACT CANCER OR GYNECOLOGIC CARCINOMA
14. gynecolog* cancer
15. gynaecolog* cancer
16. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. EXERCISE
18. exercise
19. PHYSICAL ACTIVITY
20. physical activity
21. FITNESS
22. fitness
23. YOGA
24. yoga
25. WALKING
26. walking
27. DIET
28. diet
29. NUTRITION
30. nutrition
31. diet* AND intervention
32. nutri* AND intervention
33. lifestyle intervention
34. lifestyle AND intervention
35. QUALITY OF LIFE
36. quality of life
37. life quality*
38. well being OR wellbeing
39. 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34
40. 35 OR 35 OR 36 OR 38
41. 16 AND 39 AND 40


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EXERCISE PROGRAMME IN ENDOMETRIAL CANCER: PROTOCOL OF THE FEASIBILITY AND ACCEPTABILITY SURVIVORSHIP TRIAL (EPEC-FAST)

A Smits, A Lopes, N Das, R Bekkers, L Massuger, K Galaal
British Medical Journal Open 2015;5:e009291

Abstract

Introduction

Obesity has been associated with impaired quality of life and poorer outcomes in endometrial cancer survivors. Lifestyle interventions promoting exercise and weight reduction have been proposed for survivorship care. However, studies evaluating exercise programmes for endometrial cancer survivors are lacking.

Purpose

The objective of this study is to evaluate the feasibility of an individualised exercise intervention for endometrial cancer survivors to improve quality of life.

Methods and analysis

This is a feasibility study in which women will undergo a 10-week exercise programme with a personal trainer. The study population comprises women with confirmed diagnosis of endometrial cancer, who have completed surgical treatment with curative intent and are aged 18 year or older. The study will take place at the Royal Cornwall Hospital Trust, in the UK. Feasibility will be evaluated in terms of recruitment, adherence and compliance to the programme. Secondary outcomes are quality of life, psychological distress, fatigue, pain and complication rates. In addition, the acceptability of the programme will be assessed.

Ethics and dissemination

Ethical approval was obtained through the Exeter NRES Committee. The study results will be used to optimise the intervention content, and may serve as the foundation for a larger definitive trial. Results will be disseminated through peer-review journals, congresses, relevant clinical groups and presented on the Trust website.

Background

Endometrial cancer is the most common gynaecological cancer in the United Kingdom, with 8,475 new cases being diagnosed in 2011 alone (1). Endometrial cancer has a relatively good prognosis, with a ten-year survival of 78%, resulting in a large group of long-term survivors (1). Subsequently, health related quality of life is now recognised as an important outcome for endometrial cancer survivors.

The majority of women diagnosed with endometrial cancer are obese, as excess weight is an important risk factor for endometrial cancer (2, 3). In addition, few endometrial cancer survivors meet health recommendations for physical activity (4). Obesity and inactivity have been identified as significant factors negatively influencing the quality of life of endometrial cancer survivors, surpassing the physical and psychological stress that comes with cancer diagnosis and treatment alone (5, 6). In addition, obese endometrial cancer survivors are at risk of numerous obesity-related comorbidities and possibly poorer survival (7, 8).

It has been suggested that exercise and weight reduction may be viable means to improve the quality of life and other health-related outcomes of cancer survivors (9, 10). In addition, the American College of Sports Medicine (ACSM) has recommended exercise training for cancer patients, stating it is safe and benefits functioning and quality of life (11). However, previous research has shown that endometrial cancer survivors struggle to achieve this on their own, as they do not engage in a healthy lifestyle and find it difficult to implement lifestyle changes (4, 12).

The feasibility of some lifestyle interventions including multidisciplinary counselling, behavioural change interventions and a home-based exercise programme has been demonstrated in endometrial cancer survivors (13-16). Thus far, relatively few studies have been performed to test the potential usefulness of an exercise intervention to improve the quality of life and other health outcomes of endometrial cancer survivors. In addition, the essential components and attributes of an intervention, including mode, intensity, frequency and duration of an exercise programme, have not yet been established (10, 11). To the best of our knowledge, an individualised exercise intervention has not yet been evaluated.

We, therefore, want to evaluate the feasibility of introducing an individualised exercise programme in the care for endometrial cancer survivors to improve quality of life and other health outcomes.

Methods

Design

This is a single-arm prospective feasibility study to evaluate the introduction of an individualised exercise intervention for endometrial cancer survivors. In addition, a qualitative evaluation will be performed to assess the acceptability of the intervention. The study will take place at the Royal Cornwall Hospital Trust, and has received national ethical approval through the Exeter NRES Committee.

Study population

The eligibility criteria are women older than 18 years with a diagnosis of primary endometrial cancer, undergoing surgical treatment with curative intent. Exclusion criteria are; women, presenting with recurrent endometrial cancer, those with a concurrent cancer, patients unable to give informed consent and those women undergoing palliative treatment. Women with recurrent cancer or receiving treatment in the palliative setting will not be asked to participate because of the burden of the study and as surgical treatment is usually not a standard component of palliative patient care in endometrial cancer.

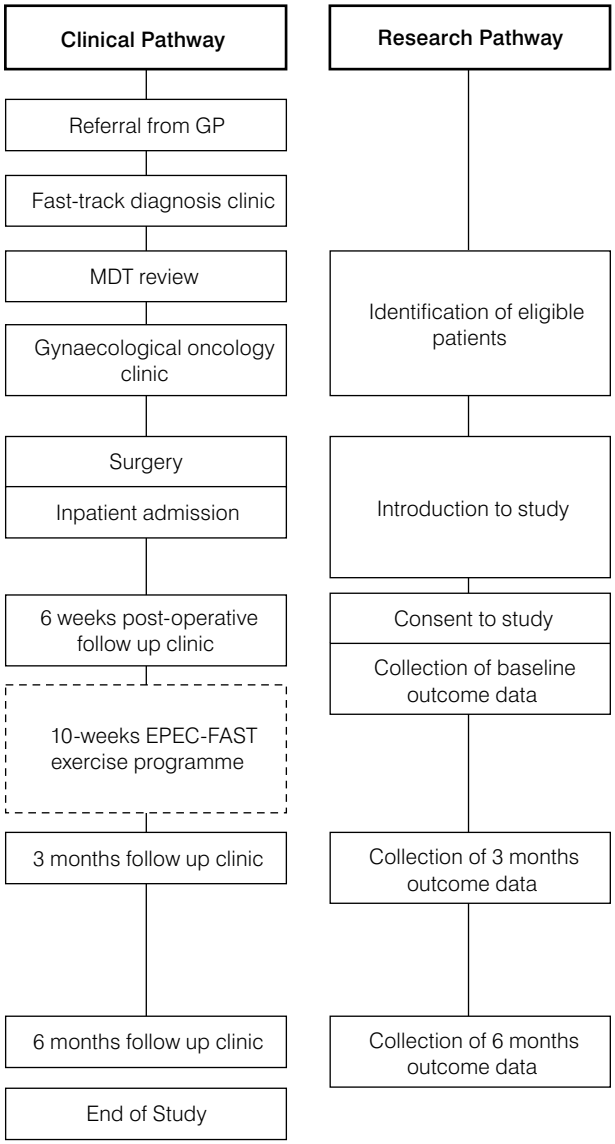
Recruitment

A member of the care team will identify potentially eligible women after confirmation of diagnosis and multidisciplinary team (MDT) review (Figure 1). Study posters will be displayed in gynaecological outpatient clinic and an information leaflet will be provided during admission for surgery. Women will be contacted one week after they have been discharged to discuss the study in detail. Women who express an interest will be seen during their post-operative check-up and consented for the study. Women will be recruited over a 12-month period; we aim to recruit a minimum of 15 patients.

Intervention

The exercise programme consists of 60-min individualised (one-to-one) training sessions with a personal trainer, once a week, for ten consecutive weeks (Table 1). The training sessions will be delivered by one personal trainer to provide consistency. The programme begins after the patient has had her six-week post-operative check-up, and will take place at a local gym facility. The programme will be tailored to the individual patient through a pre-exercise health assessment, taking into consideration their current health status, physical activity level, comorbidities and medical history. Each session consists of a 10-min warm-up, a 40-min work out, consisting of aerobic (cardiovascular) exercise, pillar strength exercise (including hip and core stability), and resistance training (muscular strength and endurance

Figure 1 Flow diagram of the clinical and research pathway of the study



training), and a 10-min cool down including flexibility training. The exercise phase will be performed at a level of 40-60% maximum heart rate (MHR), measured using a Polar Heart Rate monitor, using the Karvonen method for calculating the target heart rate interval. The resistance training will be performed at an intensity of 40-60% of one repetition maximum (1 RM). In the case of potential adverse effects such as a strain, injury or exacerbation of other symptoms, the session will be discontinued and the participant will be referred for medical attention, if needed. Participants will receive general physical activity recommendations of moderate-intensity exercise for 150 minutes per week as part of standard practise (11, 17).

Outcomes

Outcomes are assessed at baseline, at completion of the intervention, and three months after completion of the intervention. Figure 1 demonstrates the pathways of the study including data collection.

Primary outcome

The primary outcome of this study will be its feasibility aspects including; willingness of clinicians to recruit patients, number of eligible patients and recruitment rates. These will be obtained from hospital medical files, as the clinical care team will document eligibility and recruitment. Willingness of clinicians to recruit will be assessed through interviews with the clinical care team. Adherence and compliance rates to the programme will be collected from registration forms used during the exercise programme. Reasons for non-adherence or non-compliance will be identified and further addressed in the qualitative evaluation.

Secondary outcomes

Several measures evaluating possible outcomes for a definitive trial will be assessed at baseline, post-intervention (three months) and at six months to provide characteristics and standard deviations. Quality of life is evaluated through the internationally established EORTC QLQ-C30 and the QLQ-EN24 questionnaires (18, 19). The QLQ-C30 is a cancer-specific questionnaire covering several areas of quality of life; physical, role, emotional, cognitive and social functioning, as well as symptom distress and global quality of life (18). The QLQ-EN24 is a specific module for endometrial cancer patients, covering specifically relevant issues such as body image, sexuality and treatment symptoms (19). The Hospital Anxiety and Depression Scale (HADS) is used to assess psychological distress, and fatigue and pain are measured through the Brief Fatigue Inventory (BFI) and the Brief Pain Inventory (BPI) (20-22). Permissions are obtained for all measures used during the study.

Participants will receive a physical fitness assessment at baseline and at three months, which includes their current health and measuring weight and height, body

mass index (BMI), waist circumference, body fat percentage, lean muscle tissue, resting metabolism and the 6-minute walk test. The six-minute walk test will be performed on a treadmill, using an adaptation of the American Thoracic guidelines (23). Weight and BMI will also be collected at six months. Other outcomes such as adverse outcomes will be collected throughout the trial.

Qualitative evaluation

A qualitative evaluation will be undertaken after completion of the exercise programme. This will be through one-on-one telephone interviews using a moderator guide with a selected subgroup of the study population. Open-ended questions will be used to encourage reflection and elaboration on different aspects of the exercise programme. The interviews will be recorded and transcribed, and data-analysis of the interviews will occur through content analysis using simple descriptive thematic analyses, which will be performed by a researcher independent of the research delivery team (24). All data will be prospectively collected in an electronic database.

Data-collection

The quantitative measures will be collected by a member of the clinical care team at three time points; baseline, after completion of the exercise programme (three months), and three months after completion (six months). Questionnaires will be completed during standard clinical visits, which follow the same time points. The qualitative element of the study will be undertaken after completion of the exercise programme. We aim to evaluate approximately eight to ten participants through individual semi-structured interviews. This will be a purposively selected population with maximum variation in terms of age, BMI, adherence and adverse events.

Statistical analysis

Data will be presented detailing the numbers of patients that were approached, the number that were eligible and the number providing consent. As this is a feasibility study, no power calculation has been performed. Compliance rates at all stages will be presented; the number of exercise sessions undertaken (mean, median and full distribution), the numbers of questionnaires completed at each stage, and more generally the completeness of data on all outcomes at each time point. Participating patients' characteristics (demographics, comorbidities, clinical details) will be summarised and, where possible, compared with the overall population of relevant patients to explore possible factors associated with participation. Where possible, the reasons will be ascertained for potentially eligible patients not being approached to consider participation.

The questionnaire outcomes (EORTC QLQ-C30 + QLQ-EN24, HADS, BPI and BFI) will be analysed according to scoring procedures and will be linearly transformed

Table 1 The EPEC-FAST Exercise programme ©

Exercise phase*	Details
Warm-up	
10 minutes	Low intensity warm-up using an exercise bike or a treadmill.
Exercise phase	
40 minutes	***Aerobic exercise (20 minutes)*** Walking on a treadmill or cycling on an exercise bike. The exercise phase will be performed at a level of 40-60% of maximum heart rate. ***Pillar strength training (10 minutes)*** Consists of 4 exercises to improve stability and strength of the hip, and 3 exercises to improve core stability and strength. Patients are recommended to perform 8 repetitions of each of the hip stability movements per leg, and a set of 10-15 repetitions of each core muscle exercise. A stability ball may be used to facilitate some of the exercises. Hip movements: - Hip flexion - Hip extension - Hip adduction - Hip abduction Core movements: - Crunch - Back extension - Opposite arm/leg raise ***Resistance training (10 minutes)*** Consists of one set of 8 to 12 repetitions of 8 exercises that include all the major muscle groups. After initial phase repetitions, this can be increased up to 20-25 repetitions (40-60% of 1 RM) during one session. A dumbbell, stability ball or bench may be used to facilitate the exercises. Exercises: - Basic squat - Lateral raise - Dumbbell deadlift - Shoulder press - Hamstring curl - Dumbbell biceps curl - Overhead triceps extension - Calf raise
Cool down	
10 minutes	Set of 6 stretching and flexibility exercises. Four repetitions of each of the following muscle groups will be performed for 10 – 30 seconds: - Lower back - Tensor fascia lata - Hip flexor - Quadriceps - Hamstring - Calf

*: The content of the programme will subject to individual variability and will be adjusted to the individual patient.

into scales. The analysis for the outcome of quality of life, measured with the EORTC QLQ-C30 and QLQ-EN24 questionnaire is based on standard scoring procedures (25). Data will be presented on means (or medians as appropriate) and standard deviations at each time point, plus correlations and changes between baseline and follow-up scores (to inform future sample size calculations for a potential randomised trial).

Ethics and dissemination

The study results will be used to optimise the intervention content and may serve as the foundation for a larger definitive trial. We aim to disseminate the results through peer-review journals, presentation at international conferences, relevant clinical groups and results will be presented on the Trust website. Ethical approval was obtained through the Exeter NRES Committee.

Discussion

The aim of this article was to describe the protocol of a feasibility study evaluating an individualised exercise intervention in the management of endometrial cancer survivors to improve quality of life and other health related outcomes.

Research has shown that the majority of endometrial cancer survivors do not meet recommendations for physical activity, have poorer fitness and are usually overweight or obese (2, 4, 26, 27). BMI and physical activity levels have been extensively linked to the quality of life of endometrial cancer patients identifying BMI and physical activity as independent factors impacting quality of life (5, 6, 27, 28). Furthermore, it has been hypothesised that physical activity may protect from the negative impact of a higher BMI on quality of life outcomes (27).

The intervention consists of ten individualised (one-to-one) training sessions with a personal trainer at a local gym. The content of the intervention was based on national and cancer-specific recommendations of the American College of Sports Medicine, evidence from the literature and feedback from relevant patient groups (11, 17, 29, 30). The ACSM has concluded that exercise during and after cancer treatment is safe and should be encouraged, although prescriptions should be individualised according to the patient. Therefore, the EPEC-FAST programme will be tailored to the individual patient, taking into consideration their current health status, physical activity level, comorbidities and medical history though a pre-exercise medical assessment following the ACSM recommendations (11).

Unfortunately, the ACSM was unable to make recommendations for exercise interventions in gynaecological cancer patients specifically due to limited data. Therefore, general recommendations for cancer patients were followed when

developing the EPEC-FAST programme to include aerobic fitness, strength exercises (pillar strength and resistance training) and flexibility training (11). The frequency (once a week) and duration (ten weeks) of the programme were largely based on input from patient groups, as we could not find concrete guidance on essential components and attributes of an exercise programme for endometrial cancer patients in the literature (10, 11).

Important strengths of the intervention include the individualised programme and the one-to-one sessions in a private gym, which have not yet been evaluated in endometrial cancer patients. Attainable goals and individual guidance are known to improve adherence and compliance to a programme (30). We believe this is specifically applicable for endometrial cancer patients with high BMI, as they experience poorer body image and self-esteem after diagnosis and treatment (31, 32). Third, we consider the timing of the intervention to be advantageous as women are in a teachable moment, and are interested in modifying their lifestyle in hopes of achieving improved health (33, 34). In addition, the intervention fits within the current care pathway, being less burdensome for patients as they do not have to undertake additional clinical visits.

A limitation of the protocol is that the effect of the programme on overall physical activity behaviour is not assessed. We recommend this to be included as an outcome in a definitive trial, possibly through self-reported measures or objective measures such accelerometers.

Conclusion

In this article, we described the protocol of an intervention aimed at improving physical fitness, quality of life and other health outcomes in endometrial cancer survivors. In addition, we presented the study design to investigate its feasibility of delivering the intervention within the current health care model. The results of the feasibility study may be used for optimisation of the intervention and may serve as a basis for implementation of the intervention in a randomised controlled trial.

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11

GENERAL DISCUSSION

Partly from:
Body mass index and outcomes of endometrial and ovarian cancer patients
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This thesis described the effect of body mass index on treatment and quality of life outcomes of endometrial and ovarian cancer patients. It has also evaluated the current evidence on the effect of lifestyle interventions as a means to improve quality of life in gynaecological cancer patients. In addition, it presents a protocol assessing the feasibility and acceptability of an exercise programme in endometrial cancer as part of a post-treatment survivorship programme. The relevance and clinical implications of the thesis will be discussed in this chapter, along with recommendations for future research.

Endometrial cancer

Surgery is the mainstay of curative endometrial cancer treatment, followed by adjuvant therapies such as radiotherapy and/or chemotherapy in intermediate to high risk cases (1). In Chapter 2 we have shown that obese and especially morbidly obese endometrial cancer patients require longer operating times at open surgery, and that laparoscopic surgery is associated with increased conversion rates to open surgery. Furthermore, the number of post-operative complications increased with BMI, with more wound complications and antibiotics use in women with BMI ≥ 30 kg/m^2. These associations were more pronounced at open surgery, with morbidly obese patients being at highest risk.

Giugale et al. have further explored the effect of obesity in relation to surgery and reported a higher incidence of post-operative complications and higher conversion rates among the morbidly obese and super obese (BMI ≥ 50 kg/m^2) compared to the mild and moderate obese (BMI 30-39.9 kg/m^2) (2). Minimal invasive surgery was performed significantly less often in morbidly obese and super obese women. Other adverse outcomes such as blood transfusion, bowel injury, pneumonia and increased blood loss were initially associated with higher obesity classifications, but these effects were mitigated when minimal invasive procedures were performed (2).

We therefore conclude that obese women, and especially women at the extreme end of raised BMI, benefit from a minimal invasive approach in terms of post-operative outcomes. Moreover, minimal invasive surgery is associated with improved QoL outcomes compared to open surgery in endometrial cancer irrespective of BMI (3). Laparoscopic surgery should therefore be the favoured approach specifically in obese endometrial cancer patients.

Obesity is a well-known factor complicating radiation therapy in terms of positioning of the patient, set-up errors and margin requirements (4-8). However, in a relatively small study of retrospective design, we did not find any evidence to suggest that BMI is associated with increased radiation toxicities from EBRT of brachytherapy (Chapter 3). Several studies collaborate our findings, but others have reported that a higher BMI was associated with increased gynaecological and cutaneous toxicities but with less gastro-intestinal toxicities (6, 9-11). Further well designed studies would help to provide a more definitive conclusion on this association.

Ovarian cancer

We have shown that obesity does not compromise the feasibility of obtaining complete surgical cytoreduction, although obese patients may still pose significant surgical challenges (Chapter 6). Postoperatively we found that obese ovarian cancer patients had an increased risk of wound complications and a significantly prolonged hospital stay. In some cases, these complications may negatively impact recovery and delay commencement of adjuvant treatment. Therefore, specific care needs to be incorporated in the operative pathway of obese gynaecological cancer patients. This may include enhanced wound care programmes and prehabilitation programmes comprising the optimisation of patients prior to surgery.

Definitive conclusions for women with BMI ≥ 40 kg/m^2 are yet to be established, although a large study by Kumar et al. suggests that morbidly obese women with ovarian cancer have a significantly higher risk of severe operative complications (12). The morbidly and super obese have been identified as an important group at risk of adverse surgical outcomes in endometrial cancer, and future studies are needed to confirm whether these specific groups face the same challenges in ovarian cancer surgery.

Quality of life

Obesity negatively impacts QoL outcomes of endometrial and ovarian cancer survivors (Chapter 4, 7 and 8). In endometrial cancer there is ample evidence identifying increasing BMI as a negative impact, while in ovarian cancer the association between BMI and quality has received less attention. Other important outcomes such as sexual dysfunction and psychological distress and their association with BMI remain underreported in gynaecological cancer survivors, despite being well established in the general population (13-15).

It has been hypothesised that obesity negatively impacts QoL through several mechanisms. Unhealthy lifestyle behaviours including low physical activity, a poor diet and smoking, are frequently found in obese cancer patients, and have been independently linked to poorer QoL and general health outcomes (16-19). Obesity-related comorbidities such as cardiovascular disease, diabetes and osteoarthritis may further impact QoL, as do discrimination and stigmatization in personal relationships, employment and health care settings (20-24). In addition, the adverse treatment-related effects associated with increasing BMI such as surgical complications and decreased rates of minimal invasive surgery may also negatively impact the QoL of this population (3).

Although the majority of studies have assessed the effect of BMI on QoL of survivors, Doll et al. recently identified that obese gynaecological cancer patients experience poorer QoL prior to treatment compared to their non-obese counterparts (25). Interestingly, pre-treatment QoL has been associated with treatment outcomes and survival of gynaecological cancer patients (26-29). Results from the LACE trial

showed that a lower preoperative QoL was associated with severe adverse events, which persisted after correction for other known prognostic variables. Interestingly, poor QoL scores also predicted poor surgical outcomes, even in patients receiving minimal invasive surgery (26). A lower baseline QoL was also associated with increased mortality rates in ovarian patients undergoing adjuvant chemotherapy or interval secondary cytoreduction (28, 29).

Lifestyle interventions

There is considerable evidence that the QoL of cancer patients and survivors may be improved through modifiable factors such as weight and physical fitness (30, 31). Within endometrial and ovarian cancer, the current evidence reviewing lifestyle interventions is limited. In Chapter 9 we have shown that lifestyle interventions have the potential to improve several aspects of QoL and significantly reduce fatigue (32). In addition, interventions incorporating both exercise and nutrition resulted in significant weight loss and physical activity levels. In ovarian cancer, the feasibility of lifestyle interventions as a means to improve QoL has only been demonstrated by preliminary non-randomised studies.

We have shown that there is a clear need for further large prospective studies to assess the effect of lifestyle interventions on QoL outcomes of endometrial and ovarian cancer survivors. It remains unclear to what extent these outcomes can be modified, and which interventions will result in optimal improvements. The majority of studies have assessed unsupervised home-based interventions, and alternatives such as supervised individual or group sessions need to be explored (32). Moreover, there is a paucity of evidence regarding the long-term sustainability of lifestyle changes induced by these interventions, which needs to be addressed in future studies. Determining which interventions will result in a long-term healthy lifestyle is imperative for sustainable QoL improvements.

Future directions

The importance and prognostic significance of waist-hip-ratio (WHR) has recently been shown in a study based on the large NHANES III survey. The authors concluded that normal-weight central obesity defined by WHR was associated with higher total and cardiovascular mortality than BMI-defined obesity (33). The value of WHR in gynaecological cancer has mainly been assessed as a risk factor, linking an elevated WHR to an increased risk of endometrial cancer and ovarian cancer (34, 35). It would be interesting to evaluate its relation to treatment outcomes and QoL, and whether incorporating this anthropometric measure increases the prognostic significance of BMI. However, both BMI and WHR may be disputed as an appropriate measure to evaluate obesity at time of diagnosis in specifically ovarian cancer patients because of the presence of ascites or cachexia (36).

The role of physical activity has not been extensively assessed in this thesis, even though it is inextricably associated with BMI. In Chapter 8 we have shown that sedentary behaviour is an independent factor negatively influencing the QoL of ovarian cancer survivors, and has an additional detrimental effect to BMI. Other studies among ovarian and endometrial cancer patients support these findings, suggesting that improving physical activity levels is an important target for future interventions (16, 37-39). Furthermore, physical activity has been associated with an improvement in overall survival in breast and colon cancer (40, 41). The effect of lifestyle interventions on survival of women with gynaecological cancer has not yet been assessed, mainly because lifestyle behaviours have only recently emerged as important modifiable risk factors in prevention, treatment and outcomes of gynaecological cancer. Therefore, an important question that remains is whether post-diagnosis lifestyle changes such as weight loss and improved physical activity can mitigate the adverse association between obesity and poorer survival.

Chronic inflammation is known to play a role in the process of carcinogenesis and has been linked to obesity. In Chapter 5 we found that obesity is associated with higher levels of a range of inflammatory markers, and that CRP is an independent prognostic factor for overall survival of endometrial cancer patients. In addition, other studies support the prognostic value of several inflammatory markers (42-44). It would be interesting to assess whether strategies, modifying these markers would result in improved outcomes for endometrial cancer patients. It is well established that both exercise and caloric restrictions have an anti-inflammatory effect, and that they may reduce the risk, and possibly increase the survival, of several cancers (41, 45-48). Furthermore, anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDS) have been suggested to be protective for obesity-associated carcinogenesis, although data remains tentative (49).

Besides exploring new interventions, opportunities to improve general lifestyle behaviours according to national health recommendations in this population should also be explored. Following the demonstrated unhealthy lifestyle behaviours of the majority of gynaecological cancer patients, the need for education is evident and should be part of routine care (50, 51). Current counselling practices have been shown to be inadequate and incongruent with patients' needs. Only 50% of patients report receiving any lifestyle counselling, with specific recommendations rarely being offered (52). Moreover, referrals to nutritionists, weight loss programmes or bariatric specialists are rare, despite clinicians acknowledging the importance and effectiveness of such interventions (52-54). Lifestyle counselling, and especially weight loss counselling, is perceived as harmful to the doctor-patient relationship by clinicians, even though the majority of patients prefer their doctors to address weight using direct, face-to-face counselling with specific recommendations and referrals to the appropriate specialties (52, 53). After a cancer diagnosis, patients are in a

teachable moment; willing to make lifestyle modifications in hopes of achieving improved health (55, 56). Clinicians should therefore incorporate general health education and recommendation into their survivorship care, encouraging their patients to make health lifestyle changes.

The majority of studies in this thesis were of retrospective or cross-sectional design performed at one site, with one study being a two-centre cross-sectional study. To strengthen the results of our studies, we performed several systematic reviews of the literature to enhance the level of evidence. However, recognising the limitations of these studies inherent to their design, we have commenced a prospective cohort study at the Royal Cornwall Hospital Trust to further evaluate the effect of BMI on treatment modality, outcomes and QoL. Furthermore, studies assessing exercise as a possible means to improve QoL outcomes of gynaecological cancer patients are still in their infancy. We have therefore designed a feasibility trial, currently running at the Royal Cornwall Hospital Trust, which is assessing a personalised exercise intervention for endometrial cancer patients, which may serve as the foundation for a larger definitive trial (Chapter 10).

Conclusion

Obesity has a negative impact on surgical treatment in endometrial cancer, with increased rates of complications, conversion rates to open surgery, longer operating times and a prolonged hospital stay. These negative effects are more pronounced with an open surgical approach, suggesting that minimal invasive surgery may mitigate these adverse outcomes. BMI is known to impede the application of radiotherapy in endometrial cancer, but we did not find evidence that it influences radiation toxicities. New radiotherapy techniques aimed at reducing radiation exposure should be further explored, as treatment toxicities are still highly prevalent irrespective of BMI.

In ovarian cancer, obese patients have an increased risk of wound complications and a prolonged hospital stay, although obesity does not compromise the ability of obtaining complete cytoreduction nor does it negatively affect other operative outcomes.

Following treatment, BMI significantly impacts on several aspects of the QoL of survivors, with poorer global QoL, physical, social, cognitive and role functioning in obese endometrial and ovarian cancer survivors. Lifestyle intervention trials have shown promising results with regards to improving QoL through modifiable factors such as weight, diet and physical activity. However, as these interventions are still in their infancy, future research should aim to elucidate the role of lifestyle interventions on the outcomes of endometrial and ovarian cancer patients, including the long-term sustainability and effect on survival.

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SUMMARY

Summary

Endometrial cancer and ovarian cancer are the most common gynaecological cancers in the developed world and are known to be associated with obesity. The escalating obesity epidemic in countries such as the United Kingdom has resulted in the majority of endometrial and ovarian cancer patients being overweight or obese. It is crucial to determine the influence of excess weight on the outcomes of endometrial and ovarian cancer patients. Therefore, this thesis evaluated the effect of body mass index (BMI) on treatment and quality of life (QoL) outcomes of endometrial and ovarian cancer patients, and has assessed the effect of lifestyle interventions as a means to improve QoL.

Endometrial cancer

Surgery is the mainstay of curative endometrial cancer treatment. In **Chapter 2** we have assessed the effect of BMI on the surgical outcomes of endometrial cancer patients. We showed that obese and especially morbidly obese endometrial cancer patients require longer operating times with open surgery, and that laparoscopic surgery is associated with increased conversion rates to open surgery. Furthermore, the number of post-operative complications increased with a higher BMI, with more wound complications and antibiotics use in women with BMI ≥ 30 kg/m^2. These associations were more pronounced at open surgery, with morbidly obese patients being at highest risk. Other peri-operative outcomes and 30-day mortality were not associated with BMI. We therefore conclude that the laparoscopic approach should be favoured over laparotomy, especially in obese endometrial cancer patients, to improve operative and postoperative outcomes.

Radiotherapy is one of the cornerstones of adjuvant therapy in intermediate and high risk endometrial cancer. Radiation-related toxicities remain prevalent and are of particular concern for endometrial cancer patients. It is therefore important to identify possible contributing factors. In **Chapter 3** we have evaluated whether BMI has an impact on the occurrence of radiation toxicities and complications. In this relatively small retrospective study, we did not find any evidence to suggest that BMI is associated with increased radiation toxicities. However, as the current evidence is limited, larger well designed studies are needed to provide a definitive conclusion regarding the impact of BMI on radiation complications.

Quality of life issues are important outcomes for cancer patients, as cancer diagnosis and treatment have a significant impact on the quality of life. In **Chapter 4** we show that an increasing BMI has a negative impact on the quality of life outcomes of endometrial cancer patients at our institution. Furthermore, we have performed a systematic review and meta-analysis of the literature on this association, demonstrating that obese women experience significantly poorer physical functioning, social functioning,

and role functioning compared to non-obese survivors. Physical, social and role function further deteriorated significantly in the morbidly obese patients (BMI ≥ 40 kg/m^2).

Chronic inflammation is known to play a role in the process of carcinogenesis. Although, obesity causes chronic inflammation through an inflammatory response in the adipose tissue, its role in carcinogenesis remains unclear. In **Chapter 5** we have evaluated the association between inflammatory markers and obesity, and their prognostic value in endometrial cancer. In this study, obesity was associated with higher levels of a range of inflammatory markers, and specifically CRP was found to be an independent prognostic factor for overall survival in endometrial cancer patients. Further studies are needed to explore the association between BMI and inflammatory markers, and determine its exact role in the pathogenesis and prognosis of endometrial cancer.

Ovarian cancer

Surgery plays an important role in ovarian cancer management and is usually extensive, as complete cytoreduction (removal of all visible disease) is an important prognostic factor for survival. The impact of BMI on the surgical treatment and outcomes of ovarian cancer surgery has been described in **Chapter 6**. We found that obesity does not compromise the feasibility of obtaining complete cytoreduction, although obese patients may still pose significant surgical challenges. Obese ovarian cancer patients did have an increased risk of wound complications and a significantly prolonged hospital stay. Definitive conclusions for women with BMI ≥ 40 kg/m^2 are yet to be established, but our results suggest that morbidly obese women have a significantly higher risk of severe operative complications such as organ failure. Other surgical complications and 30-day mortality were not affected by BMI.

Thus far, the relation between BMI and QoL has received limited attention in ovarian cancer, despite the majority of patients being overweight or obese. In **Chapter 7 and 8** we have described the detrimental effect of excess weight on the QoL outcomes of ovarian cancer survivors. Obese survivors experience significantly poorer global QoL, physical, cognitive and social functioning and they report more fatigue and a poorer body image. No conclusions could be provided regarding the morbidly obese, as only a minority of women studied had a BMI ≥ 40 kg/m^2.

BMI and physical activity are inextricably associated and the majority of ovarian cancer patients do not meet the national health recommendations for physical activity. In **Chapter 8** we assessed the effect of physical activity on the QoL of ovarian cancer survivors, showing that sedentary behaviour is an independent factor negatively influencing QoL, and has an additional detrimental effect to BMI.

Lifestyle interventions

Within endometrial and ovarian cancer, the current evidence reviewing lifestyle interventions is limited. In **Chapter 9** we have shown that lifestyle interventions have the potential to improve several aspects of QoL and significantly reduce fatigue. The interventions assessed in our review included single-mode exercise programmes or a combination of both exercise and nutrition. In endometrial cancer patients, lifestyle interventions may improve physical functioning, fatigue, self-efficacy and sleep dysfunction. In addition, interventions incorporating both exercise and nutrition resulted in significant weight loss and physical activity levels. In ovarian cancer, the feasibility of lifestyle interventions as a means to improve QoL has only been demonstrated by preliminary non-randomised studies, suggesting that these interventions may result in QoL improvements. However, the effect of lifestyle interventions on QoL outcomes of endometrial and ovarian cancer patients, needs to be further assessed. In addition, the majority of studies assessed unsupervised home-based interventions, and alternatives such as supervised individual or group sessions need to be explored.

This has led us to the development of a feasibility intervention study assessing a personalised exercise intervention for endometrial cancer patients, which is outlined in **Chapter 10**. The study is currently running at the Royal Cornwall Hospital Trust, and may serve as the foundation for a larger definitive trial.

Finally, we have outlined the results of this thesis and placed our outcomes into context using the literature (**Chapter 11**). In addition, we have provided clinical recommendations and discussed possible directions for future research.

SAMENVATTING

Samenvatting

De obesitas-epidemie heeft ertoe geleid dat meer dan de helft van de mensen in het Verenigd Koninkrijk overgewicht heeft, van wie 25% kampt met obesitas. Verwacht wordt dat ook andere Europese landen te maken krijgen met een duidelijke stijging van het aantal mensen met obesitas. Baarmoeder(endometrium)kanker en eierstok-(ovarium)kanker zijn beide geassocieerd met obesitas, met als gevolg dat de incidentie van deze ziekten toeneemt. Tegelijkertijd kampt een groot deel van deze patiëntenpopulatie met overgewicht of obesitas. Endometrium- en ovariumkanker zijn momenteel de meest voorkomende soorten gynaecologische kanker in Europa en ze treffen jaarlijks meer dan 15.500 vrouwen in het Verenigd Koninkrijk. Het is daarom cruciaal om inzicht te krijgen in het effect van obesitas op de behandeling en uitkomsten van deze groeiende patiëntengroep. In dit proefschrift is de invloed van Body Mass Index (BMI) op de behandeling en kwaliteit van leven van patiënten met endometrium- en ovariumkanker onderzocht.

Endometriumkanker

Chirurgie is een belangrijke pijler van de behandeling van endometriumkanker. In **hoofdstuk 2** hebben wij de invloed van een verhoogde BMI op de chirurgische behandeling en uitkomsten van endometriumkanker onderzocht. Hieruit bleek dat de operatieduur bij open buikoperaties gemiddeld langer is bij vrouwen met een BMI $\geq$ 30 kg/m^2 dan vrouwen met BMI $<$ 30 kg/m^2. Bovendien wordt bij de eerstgenoemde groep vaker een minimaal invasieve benadering (kijkoperatie) omgezet naar een open buik operatie. Dit is nadelig voor de patiënt omdat langere operaties gepaard gaan met toenemende stress en een verhoogd risico op complicaties. Daarbij betekent een open buikoperatie vaak een langer en moeizamer herstel, waarbij het risico op postoperatieve complicaties hoger is dan bij een kijkoperatie. Een andere belangrijke uitkomst van de studie is dat vrouwen met een BMI $\geq$ 30 kg/m^2 een hoger risico hebben op postoperatieve complicaties in vergelijking met vrouwen met een normaal gewicht of overgewicht (BMI $<$ 30 kg/m^2). Dit verschil is met name uitgesproken onder vrouwen die een open buikoperatie ondergaan, waarbij obesitas geassocieerd is met meer wondcomplicaties en antibioticagebruik. Vrouwen met extreme obesitas (BMI $\geq$ 40 kg/m^2) lopen hierbij het grootste risico. Hieruit hebben wij geconcludeerd dat een minimaal invasieve benadering (kijkoperatie) moet worden nagestreefd bij obese vrouwen om het verhoogde risico op postoperatieve complicaties te reduceren.

Radiotherapie is een belangrijk onderdeel van de adjuvante behandeling van endometriumkanker. Deze wordt in de vorm van uitwendige therapie, inwendige/vaginale therapie of een combinatie hiervan gegeven. Radiotherapie heeft als doel het risico op locoregionale recidieven te reduceren, maar heeft geen effect op de

overlevingskans en staat daarom nog steeds ter discussie. Omdat radiotherapie vaak gepaard gaat met complicaties, is het essentieel om factoren die van invloed zijn te identificeren. In **hoofdstuk 3** hebben wij onderzocht of obesitas geassocieerd is met complicaties bij verschillende vormen van radiotherapie. Uit onze retrospectieve studie bleek dat obesitas niet van invloed is op de incidentie van complicaties ten gevolge van radiotherapie, in tegenstelling tot de resultaten van sommige andere studies. Nieuwe studies zijn daarom noodzakelijk om het effect van obesitas verder te evalueren.

Kwaliteit van leven is een belangrijke uitkomst voor kankerpatiënten. Het is welbekend dat overgewicht in de gezonde populatie de kwaliteit van leven negatief beïnvloedt maar het effect hiervan op endometriumkankerpatiënten is minder evident. In **hoofdstuk 4** tonen wij aan dat een hoger BMI een nadelig effect heeft op de kwaliteit van leven van patiënten van het Royal Cornwall Hospital Trust. Onze resultaten worden ondersteund door verscheidene studies die zijn gebundeld in een meta- analyse. Vrouwen met een BMI ≥ 30 kg/m^2 ervaren een slechtere kwaliteit van leven in de vorm van een verminderd fysiek functioneren, sociaal functioneren en rolfunctioneren (dagelijkse bezigheden). Deze domeinen verslechteren significant naarmate het BMI verder stijgt (BMI ≥ 40 kg/m^2).

Obesitas veroorzaakt een chronische ontsteking door een inflammatoire reactie in adipeus weefsel. Dit wordt gekenmerkt door een infiltratie van ontstekingscellen zoals lymfocyten en myeloide cellen. Chronische inflammatie speelt een rol in de carcinogenese van endometriumkanker, maar de rol van obesitas hierin is nog onduidelijk. Obesitas is geassocieerd met een toename van verschillende ontstekingscellen in het bloed van patiënten met endometriumkanker (**hoofdstuk 5**). Vooral het C-reactief proteïne (CRP) was duidelijk verhoogd bij obese patiënten en bleek van prognostische waarde waarbij een preoperatief CRP ≥ 5.0 (mg/L) geassocieerd was met een slechtere overleving. De rol en voorspellende waarde van preoperatieve biomarkers dient daarom verder onderzocht te worden.

Ovariumkanker

Chirurgie neemt ook een centrale plaats in bij de behandeling van ovariumkanker. Dit zijn vaak uitgebreide operaties omdat bij de meerderheid de kanker in een vergevorderd stadium wordt gediagnosticeerd. Het primaire doel is het behalen van complete debulking (verwijdering van al het zichtbare tumorweefsel), aangezien dit de overlevingskans van de patiënt vergroot. De impact van obesitas op de uitkomsten en complicaties van chirurgische behandeling van patiënten met ovariumkanker is onderzocht in **hoofdstuk 6**. Obesitas heeft geen nadelige invloed op het behalen van complete debulking, al kan het de moeilijkheidsgraad van de operatie verhogen. Obese patiënten hebben wel een verhoogd risico op wondcomplicaties en een langere opnameduur in vergelijking tot patiënten met een BMI ≤ 30 kg/m^2. Vrouwen

met morbide obesitas (BMI ≥ 40 kg/m^2) hebben een verhoogd risico op ernstige complicaties waaronder orgaanfalen, al is deze specifieke patiëntengroep slechts in twee studies is onderzocht. Andere belangrijke uitkomsten zoals de 30-dagen-mortaliteit worden niet negatief beïnvloed door obesitas.

Het effect van overgewicht op de kwaliteit van leven van patiënten met ovariumkanker heeft tot dusver weinig aandacht gekregen. Doormiddel van twee institutionele studies hebben wij geconcludeerd dat een hogere BMI geassocieerd is met een verminderde kwaliteit van leven (**hoofdstuk 7 en 8**). Obese patiënten met ovariumkanker ervaren een slechtere kwaliteit van leven, met onder andere een verminderd fysiek, cognitief en sociaal functioneren, en geven blijk van meer vermoeidheid en een slechter lichaamsbeeld. We konden geen conclusies trekken bij patiënten met een BMI ≥ 40 kg/m^2, aangezien dit slechts een kleine subgroep van de populatie betrof. Verder onderzoek is nodig om het effect van extreme obesitas op de kwaliteit van leven van patiënten met ovariumkanker te evalueren.

Obesitas en verminderde lichaamsbeweging zijn onlosmakelijk met elkaar verbonden. De meerderheid van patiënten met ovariumkanker voldoet niet aan de bewegingsvoorschriften van nationale richtlijnen. In **hoofdstuk 8** is daarom de rol van lichaamsbeweging op de kwaliteit van leven onderzocht, waaruit naar voren kwam dat sedentair gedrag een onafhankelijke risicofactor is naast BMI.

Leefstijlinterventies

Verschillende onderzoeken suggereren dat BMI en lichaamsbeweging modificeerbare factoren zijn om de kwaliteit van leven van kankerpatiënten te verbeteren. In **hoofdstuk 9** presenteren we een literatuuronderzoek over het effect van leefstijlinterventies ter verbetering van de kwaliteit van leven van patiënten met endometrium- en ovariumkanker, nadat zij hun behandeling hebben voltooid. Hieruit bleek dat leefstijlinterventies de potentie hebben om verschillende aspecten van kwaliteit van leven te verbeteren. De geïncludeerde studies onderzochten een verscheidenheid aan interventies variërend van beweging tot voeding, of een combinatie hiervan. Patiënten met endometriumkanker rapporteerden een verbetering in fysiek functioneren, zelfeffectiviteit en slaapstoornissen. Daarbij leiden interventies bestaande uit een combinatie van beweging en dieet tot significant gewichtsverlies en toegenomen lichaamsbeweging. Ten aanzien van ovariumkanker is er een beperkt aantal preliminaire niet-gerandomiseerde studies die suggereren dat leefstijlinterventies verschillende aspecten van kwaliteit van leven bevorderen. Verdere bewijsvoering voor het effect van leefstijlinterventies in de patiënten met endometrium- en ovariumkanker is echter noodzakelijk. De meerderheid van de onderzoeken evalueerde ongesuperviseerde interventies in de thuisomgeving. Alternatieven waaronder gesuperviseerde interventies in de vorm van individuele sessies of groepssessies moeten nog nader worden onderzocht. Dit heeft ertoe geleid dat wij een studieprotocol hebben ontwikkeld voor een

geïndividualiseerd bewegingsprogramma onder directe supervisie van een personal trainer (**hoofdstuk 10**). De pilotstudie loopt momenteel in het Royal Cornwall Hospital Trust in het Verenigd Koninkrijk, en zal mogelijk als basis fungeren voor een groter gerandomiseerd onderzoek.

In **hoofdstuk 11** worden de resultaten van de verschillende studies in dit proefschrift bediscussieerd en onze bevindingen vergeleken met de literatuur. Hierbij hebben we enkele aanbevelingen voor de klinische praktijk en toekomstig onderzoek geformuleerd.

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Dankwoord

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LIST OF PUBLICATIONS

List of publications

A Smits, A Lopes, R Bekkers, L Massuger, K Galaal. Body mass index and outcomes of endometrial and ovarian cancer patients. Expert Review of Quality of Life in Cancer Care, 2016;1(3):221-229

A Smits, A Lopes, N Das, A Kumar, W Cliby, E Smits, R Bekkers, L Massuger, K Galaal BMI and surgical outcomes in ovarian cancer patients – the role of obesity. BJOG 2016;123:300-308

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Submitted

A Smits, J McGrane, A Lopes, N Simpson, E Kent, R Bekkers, L Massuger, K Galaal. BMI and radiotherapy toxicities in endometrial cancer: are obese women at a disadvantage?

A Smits, S Knox, A Lopes, J Palmer, R Bekkers, L Massuger, K Galaal. The prognostic significance of pre-operative biomarkers in endometrial cancer: does BMI play a role?

CURRICULUM VITAE

Curriculum Vitae

Anke Smits werd op 2 februari 1989 geboren te Nijmegen, als eerste kind van Martien en Annelies Smits. Ze groeide op in het Brabantse Nistelrode en behaalde haar eindexamen VWO in 2007 aan het Maasland College te Oss.

Ze kon direct starten aan de opleiding Geneeskunde aan de Radboud Universiteit te Nijmegen. Binnen drie jaar behaalde zij haar bachelor, wat gepaard ging met een gezellige studententijd gecombineerd met verre reizen. In 2010 startte ze met haar coschappen en al snel ontdekte ze dat haar hart lag bij de gynaecologie en obstetrie. De coschappen werden afgesloten met een seniorcoschap gynaecologie in het Dr. Horacio E. Oduber Hospitaal te Aruba waar haar enthousiasme voor het vak werd bevestigd. Op aanraden van dr. R.L.M. Bekkers ging Anke voor haar onderzoekstage naar het Royal Cornwall Hospital Trust te Truro in het Verenigd Koninkrijk, waar ze dankzij dr. K. Galaal en dr. A. Lopes door het onderzoekvirus werd gegrepen. Na het behalen van haar artsenbul in december 2013 verhuisde ze met haar partner Piet naar Truro waar ze gedurende twee jaar onderzoek verrichtte, gecombineerd met klinisch werk in de gynaecologische oncologie. In februari 2016 is Anke begonnen als arts-assistent in het Rijnstate ziekenhuis in Arnhem, waarna ze hoopt haar carrière als gynaecoloog in opleiding te kunnen vervolgen.